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(54) **Imidazopyridine compounds and processes for preparation thereof.**

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Description

The present invention relates to novel imidazopyridine compounds and pharmaceutically acceptable salt thereof. More particularly, it relates to novel imidazopyridine compounds and pharmaceutically acceptable salts thereof which have antiulcerative activity, to processes for preparation thereof, to pharmaceutical composition comprising the same, and to method of using the same therapeutically in the treatment of ulcer in human being or animals.

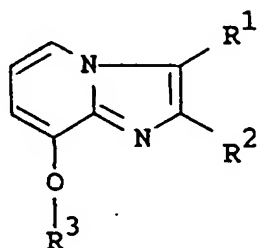
Accordingly, one object of the present invention is to provide novel imidazopyridine compounds and pharmaceutically acceptable salt thereof, which are useful as a medicine for ulcer.

Another object of the present invention is to provide processes for preparation of said imidazopyridine compounds and pharmaceutically acceptable salts thereof.

A further object of the present invention is to provide pharmaceutical composition comprising, as an active ingredient, said imidazopyridine compounds or its pharmaceutically acceptable salt.

Still further object of the present invention is to provide method of using said imidazopyridine compounds or its pharmaceutically acceptable salt in the treatment of ulcer in human being or animal.

The imidazopyridine compounds of the present invention are novel and can be represented by the formula (I) :



(I)

wherein

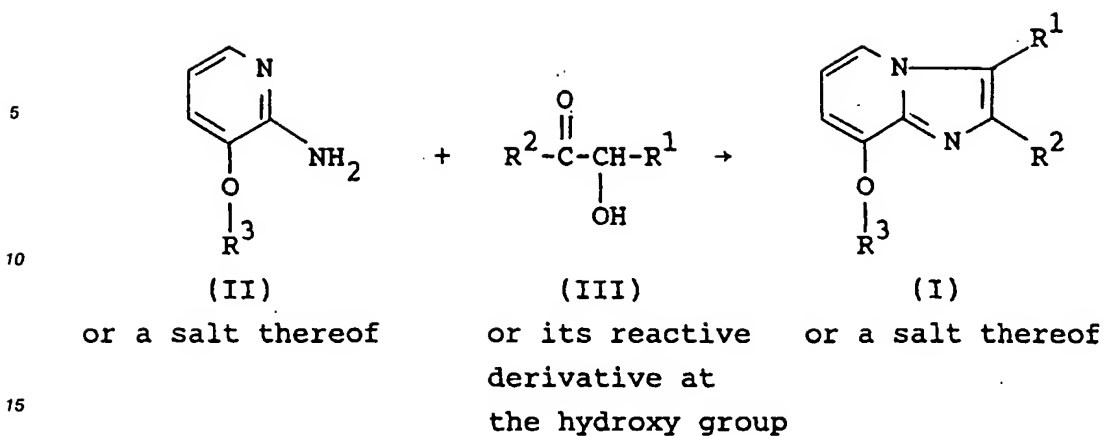
R¹ is C₂-C₆ alkynyl,

R² is C₁-C₆ alkyl, and

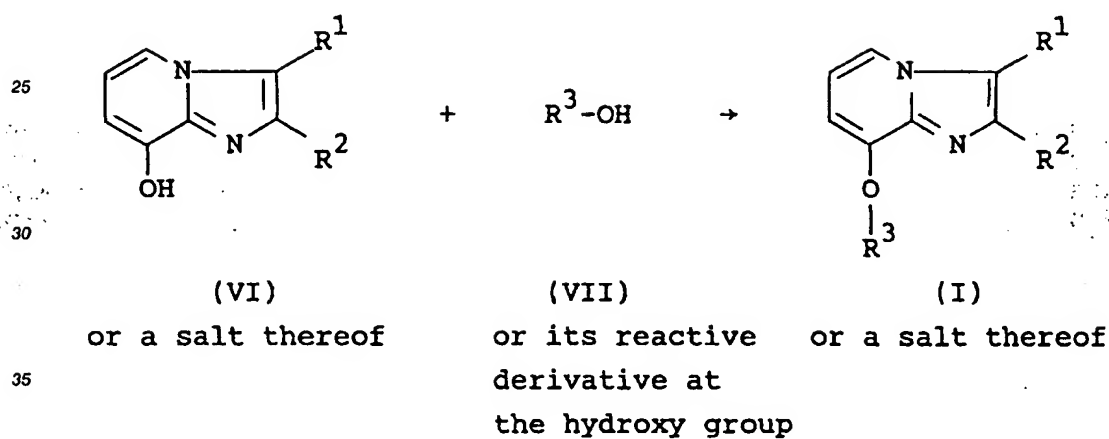
R³ is benzyl substituted by C₁-C₆ alkyl and one additional substituent selected from C₁-C₆ alkanoylamino, C₁-C₆ alkanesulfonylamino, C₁-C₆ alkoxy-carbonylamino, isonicotinamido, ureido, ureido having C₁-C₆ alkyl, C₁-C₆ alkoxy-carbonylamino(C₁-C₆)alkanoylamino, phenyl(C₁-C₆)alkoxy-carbonylamino, 3-benzoylthioureido, thioureido, C₁-C₆ alkanoyloxy(C₁-C₆)alkanoylamino, C₁-C₆ alkanoylcarbonylamino C₁-C₆ alkoxy-carbonylcarbonylamino, sulfamido, C₁-C₆ alkanoylamino having hydroxy and amino(C₁-C₆)alkanoylamino.

According to the present invention, the object compounds(I) can be prepared by the following processes.

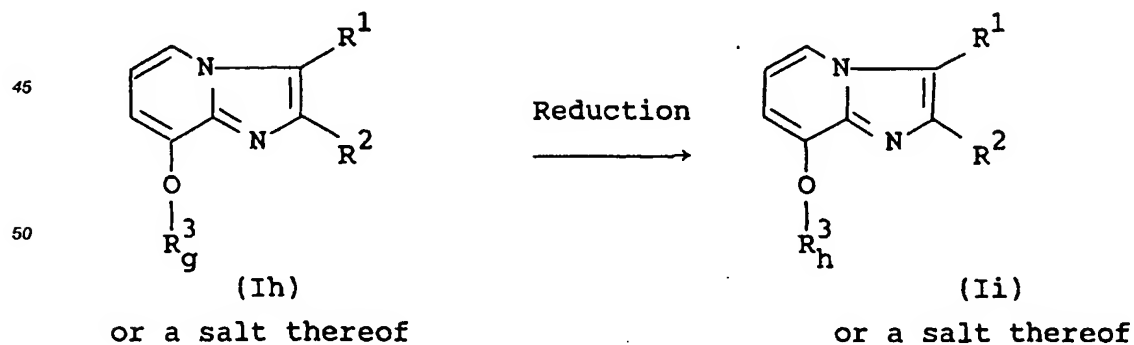
Process 1



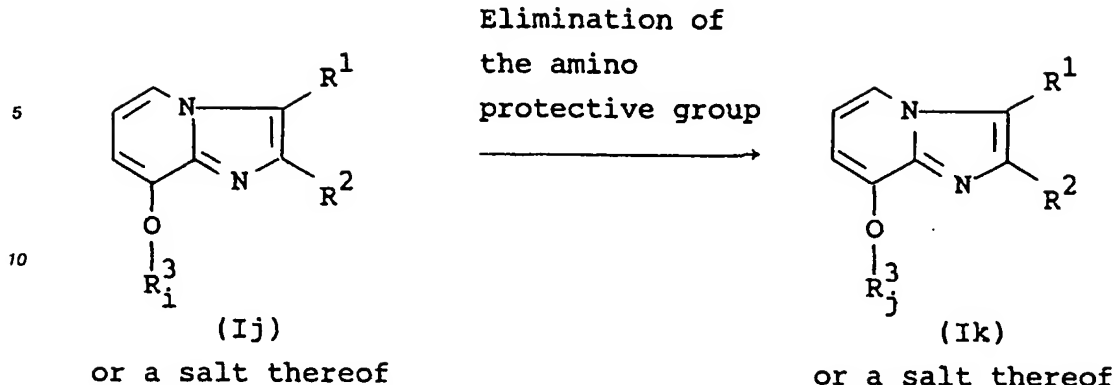
20 Process 2



40 Process 3



55 Process 4



wherein

- R^1 , R^2 and R^3 are each as defined above,
- R_g^3 is benzyl substituted by C_1 - C_6 alkyl and C_1 - C_6 alkanoylcarbonylamino,
- R_h^3 is benzyl substituted by C_1 - C_6 alkyl and α -hydroxy(C_1 - C_6)alkanoylamino,
- R_i^3 is benzyl substituted by C_1 - C_6 alkyl and one additional substituent selected from C_1 - C_6 alkoxycarbonylamino(C_1 - C_6)alkanoylamino and 3-benzoylthioureido, and
- R_j^3 is benzyl substituted by C_1 - C_6 alkyl and one additional substituent selected from amino(C_1 - C_6)alkanoylamino and thioureido.

As to the starting compounds (II), (III), (VI) and (VII), some of them are novel and can be prepared by the procedures disclosed in the following Preparations 1 to 17.

Suitable salts of the object compounds (I) are conventional non-toxic, pharmaceutically acceptable salts and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, cesium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.); and the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

Suitable " C_2 - C_6 alkynyl" group and " C_2 - C_6 alkynyl" moieties may be the ones having 2 to 6 carbon atoms and may include ethynyl, 1(or 2)-propynyl, 1(or 2 or 3)-butynyl, 1(or 2 or 3 or 4)-pentylnyl, 1(or 2 or 3 or 4 or 5)-hexynyl, and the like.

Suitable " C_1 - C_6 alkyl" group and " C_1 - C_6 alkyl" moieties may be the ones having 1 to 6 carbon atom(s) and may include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, pentyl, hexyl and the like.

Suitable "benzyl substituted by C_1 - C_6 alkyl and C_1 - C_6 alkanoylamino" may include benzyl substituted by methyl and C_1 - C_6 alkanoylamino (e.g. 6-formamido-2-methylbenzyl, 3-acetamido-2-methylbenzyl, 5-acetamido-2-methylbenzyl, 2-acetamido-6-methylbenzyl, 2-methyl-6-propionamidobenzyl, 2-acetamido-4-methylbenzyl, 2-butyramido-6-methylbenzyl, etc.), and the like.

Suitable "benzyl substituted by C_1 - C_6 alkyl and C_1 - C_6 alkanesulfonylamino" may include benzyl substituted by methyl and C_1 - C_6 alkanesulfonylamino (e.g. 2-methanesulfonylamino-6-methylbenzyl, etc.) and the like.

Suitable "benzyl substituted by C_1 - C_6 alkyl and C_1 - C_6 alkoxycarbonylamino" may include benzyl substituted by methyl and C_1 - C_6 alkoxycarbonylamino (e.g. 2-methoxycarbonylamino-6-methylbenzyl, 2-ethoxycarbonylamino-6-methylbenzyl, 2-methyl-6-i-propoxycarbonylamino-6-methylbenzyl, 2-t-butoxycarbonylamino-6-methylbenzyl, etc.) and the like.

Suitable "benzyl substituted by C_1 - C_6 alkyl and C_1 - C_6 alkanoylcarbonylamino" may include benzyl substituted by methyl and C_1 - C_6 alkanoylcarbonylamino (e.g. 2-methyl-6-pyruvamidobenzyl, etc.), and the

like.

Suitable "benzyl substituted by C₁-C₆ alkyl and α -hydroxy(C₁-C₆)alkanoylamino" may include benzyl substituted by methyl and α -hydroxy(C₁-C₆)alkanoylamino (e.g. 2-lactamido-6-methylbenzyl, etc.), and the like.

5 Suitable "benzyl substituted by C₁-C₆ alkyl and C₁-C₆ alkoxy-carbonylamino(C₁-C₆)alkanoylamino" may include benzyl substituted by methyl and C₁-C₆ alkoxy-carbonylamino(C₁-C₆)alkanoylamino (e.g. 2-t-butoxycarbonylaminoacetamido-6-methylbenzyl, etc.), and the like.

Suitable "benzyl substituted by C₁-C₆ alkyl and amino(C₁-C₆)alkanoylamino" may include benzyl substituted by methyl and amino(C₁-C₆)alkanoylamino (e.g. 2-aminoacetamido-6-methylbenzyl, etc.), and the like.

10 Suitable "benzyl substituted by C₁-C₆ alkyl and 3-benzoylthioureido" may include benzyl substituted by methyl and 3-benzoylthioureido (e.g. 2-(3-benzoylthioureido)-6-methylbenzyl, etc.), and the like.

Suitable "benzyl substituted by C₁-C₆ alkyl and thioureido" may include benzyl substituted by methyl and thioureido (e.g. 2-methyl-6-thioureidobenzyl, etc.) and the like.

15 Suitable "benzyl substituted by C₁-C₆ alkyl and isonicotinamido" may include benzyl substituted by methyl and isonicotinamido (e.g. 2-isonicotinamido-6-methylbenzyl, etc.) and the like.

Suitable "benzyl substituted by C₁-C₆ alkyl and ureido" may include benzyl substituted by methyl and ureido (e.g. 2-methyl-6-ureidobenzyl, etc.), and the like.

Suitable "benzyl substituted by C₁-C₆ alkyl and ureido having C₁-C₆ alkyl" may include benzyl substituted by methyl and ureido having C₁-C₆ alkyl (e.g. 6-methyl-2-(3-methylureido)benzyl, etc.), and the like.

Suitable "benzyl substituted by C₁-C₆ alkyl and phenyl(C₁-C₆)alkoxy-carbonylamino" may include benzyl substituted by methyl and phenyl(C₁-C₆)alkoxy-carbonylamino (e.g. 2-benzoyloxy-carbonylamino-6-methylbenzyl, etc.), and the like.

25 Suitable "benzyl substituted by C₁-C₆ alkyl and C₁-C₆ alkanoyloxy(C₁-C₆)alkanoylamino" may include benzyl substituted by methyl and C₁-C₆ alkanoyloxy(C₁-C₆)alkanoylamino (e.g. 2-acetoxyacetamido-6-methylbenzyl, etc.), and the like.

Suitable "benzyl substituted by C₁-C₆ alkyl and C₁-C₆ alkoxy-carbonyl-carbonylamino" may include benzyl substituted by methyl and C₁-C₆ alkoxy-carbonyl-carbonylamino (e.g. 2-methoxalylamino-6-methylbenzyl, etc.), and the like.

30 Suitable "benzyl substituted by C₁-C₆ alkyl and sulfamido" may include benzyl substituted by methyl and sulfamido (e.g. 2-methyl-6-sulfamidobenzyl, etc.), and the like.

Suitable "benzyl substituted by C₁-C₆ alkyl and C₁-C₆ alkanoylamino having hydroxy" may include benzyl substituted by methyl and C₁-C₆ alkanoylamino having hydroxy (e.g. 2-hydroxyacetamido-6-methylbenzyl, 2-lactamido-6-methylbenzyl, etc.), and the like.

35 The processes for preparing the object compounds of the present invention are explained in detail in the following.

Process 1

40 The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (III) or its reactive derivative at the hydroxy group.

Suitable salts of the compound (II) can be referred to the acid addition salt as exemplified for the compound (I), and suitable reactive derivative of the compound (III) may be one, in which the hydroxy group is replaced by an acid residue such as halogen (e.g. fluorine, chlorine, bromine, iodine), acyloxy (e.g. acetoxy, tosyloxy, mesyloxy, etc.), and the like.

This reaction is usually carried out in a solvent such as alcohol [e.g. methanol, ethanol, etc.], benzene, N,N-dimethylformamide, tetrahydrofuran, diethyl ether or any other solvent which does not adversely affect the reaction.

50 The reaction may be carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide [e.g. sodium hydroxide, potassium hydroxide, etc.], an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], an alkali metal bicarbonate [e.g. sodium bicarbonate, potassium bicarbonate, etc.], tri(lower)alkylamine [e.g. trimethylamine, triethylamine, etc.], pyridine or its derivative [e.g. picoline, lutidine, 4-dimethylaminopyridine, etc.], or the like. In case that the base to be used is liquid, it can also be used as a solvent.

55 In case that the compound (III) is used in a form of free hydroxy, the reaction can be carried out in the presence of a condensing agent such as N,N-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-

diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxycetylene; 1-alkoxy-1-chloroethylene; 1,1'-(carbonyldioxy)dibenzotriazole, 1,1'-dibenzotriazolyloxallate trialkylphosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride);
 5 phosphorus trichloride; thionyl chloride; oxalyl chloride; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of dimethylformamide with thionyl chloride, phosgene, phosphorus oxychloride, etc.; or the like.

The reaction temperature is not critical, and the reaction can be carried out under cooling, at ambient
 10 temperature or under warming or heating.

Process 2

The object compound (I) or a salt thereof can be prepared by reacting the compound (VI) or a salt
 15 thereof with the compound (VII) or its reactive derivative at the hydroxy group.

Suitable salts of the compound (VI) can be referred to the salt as exemplified for the compound (I) and suitable reactive derivative of the compound (VII) may be the same as those given for the compound (III) in Process 1.

This reaction is usually carried out in a solvent such as alcohol [e.g. methanol, ethanol, etc.], benzene,
 20 N,N-dimethylformamide, tetrahydrofuran, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction may be carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide [e.g. sodium hydroxide, potassium hydroxide, etc.], an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], an alkali metal bicarbonate [e.g. sodium bicarbonate, potassium
 25 bicarbonate, etc.], tri(lower)alkylamine [e.g. trimethylamine, triethylamine, etc.], pyridine or its derivative [e.g. picoline, lutidine, 4-dimethylaminopyridine, etc.], or the like. In case that the base to be used is liquid, it can also be used as a solvent.

The reaction temperature is not critical, and the reaction can be carried out under cooling, at ambient
 temperature or under warming or heating.

30

Process 3

The object compound (II) or a salt thereof can be prepared by reducing a compound (Ih) or a salt thereof.

The reduction can be carried out in a conventional manner, namely, chemical reduction or catalytic
 35 reduction.

Suitable reducing agents to be used in chemical reduction are a metal hydride compound such as aluminum hydride compound [e.g. lithium aluminum hydride, sodium aluminum hydride, aluminum hydride, lithium trimethoxyaluminum hydride, lithium tri-t-butoxyaluminum hydride, etc.], borohydride compound [e.g.
 40 sodium borohydride, lithium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, etc.], borane, diborane, aluminum halide [e.g. aluminum chloride, etc.], phosphorus trihalide [e.g. phosphorus trichloride, phosphorus tribromide, etc.], ferrous oxalate, a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric
 45 acid, hydrobromic acid, etc.] or the like.

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalyst [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalyst [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal
 palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalyst [e.g. reduced
 50 nickel, nickel oxide, Raney nickel, etc.], cobalt catalyst [e.g. reduced cobalt, Raney cobalt, etc.], iron catalyst [e.g. reduced iron, Raney iron, etc.], copper catalyst [e.g. reduced copper, Raney copper, Ullman copper, etc.] or the like.

The reaction of this process is usually carried out in a solvent such as water, alcohol [e.g. methanol, ethanol, propanol, etc.], acetic acid, diethyl ether, dioxane, tetrahydrofuran, methylene chloride, chloroform,
 55 N,N-dimethylformamide, dimethylsulfoxide, or any other organic solvent which does not adversely influence the reaction or a mixture thereof.

The reaction is preferably carried out under somewhat milder conditions such as under cooling to warming.

Process 4

The object compound (Ik) or a salt thereof can be prepared by subjecting the compound (Ij) or a salt thereof to elimination reaction of the amino protective group in R_1^3 .

5 Suitable salts of the compound (Ij) and (Ik) can be referred to the salts as exemplified for the compound (I).

Suitable method for this elimination reaction may include conventional one such as hydrolysis, reduction, or the like. The hydrolysis is preferably carried out in the presence of a base or an acid.

Suitable base may include, for example, an inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal acetate (e.g. sodium acetate, potassium acetate, etc.), alkaline earth metal phosphate (e.g. magnesium phosphate, calcium phosphate, etc.), alkali metal hydrogen phosphate (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate, etc.), or the like, and an organic base such as trialkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo[4,3,0]non-5-one, 1,4-diazabicyclo[2,2,2]octane, 1,5-diazabicyclo[5,4,0]undecene-5 or the like. The hydrolysis using a base is often carried out in water or a hydrophilic organic solvent or a mixed solvent thereof.

20 Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.).

The present hydrolysis is usually carried out in an organic solvent, water or a mixed solvent thereof.

The reaction temperature is not critical, and it may suitably be selected in accordance with the kind of the hydroxy protective group and the elimination method.

25 The object compounds (I) and their pharmaceutically acceptable salts of the present invention are novel and exhibit high inhibitory activity on ulcer.

In order to illustrate the usefulness of the object compound (I), the pharmacological data of the representative compound of the object compound (I) are shown in the following.

30 (A) Inhibition on ethanol ulcer

Test Method :

Five male Sprague-Dawley rats, aged 7 weeks and weighing about 200 g, were used per group for the study on ethanol ulcer after the fast for 24 hours.

Test compound was suspended in 0.1% methylcellulose aqueous solution, and the suspension (5 ml/kg) was orally given to each rat.

The control group was given a vehicle, i.e. 0.1% methylcellulose aqueous solution (5 ml/kg), alone in the same way.

40 Absolute ethanol (5 ml/kg) was orally administered 30 minutes after dosing with test compound, and one hour later, the rats were sacrificed and their stomachs were removed. The area of ulcers of each rat was measured. The mean area (mm²) in the medicated group was compared with that in the control group.

Test Compound

45 (1) 8-(2-Methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

Test Result

50

Inhibition % at the dose of 32 mg/kg :	
Test Compound	Inhibition %
(1)	93.2

55

(B) Inhibition on stress ulcer

Test Method :

Five Sprague-Dawley rats weighing about 200 g were used per group. Each animal was immobilized in a small cage and put in a water bath allowing to respire. The temperature of the water bath kept at 22 ° C. The test compound was administered orally just before the immobilization. Seven hours later, the animals were sacrificed and their stomachs were removed. The stomach was then fixed with 2% formalin. The area of ulcers was measured for each animal. The mean area (mm²) in the medicated animals was compared with that in the control animals.

Test Compounds

- (1) 8-(2-Methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
- (2) 8-(2-Acetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
- (3) 2-Methyl-8-(2-methyl-6-ureidobenzyloxy)-3-(2-propynyl)imidazo[1,2-a]pyridine
- (4) 2-Methyl-8-(2-methyl-6-thioureidobenzyloxy)-3-(2-propynyl)imidazo[1,2-a]pyridine

Test Result

Inhibition % at the dose of 32 mg/kg :	
Test Compound	Inhibition %
(1)	100
(2)	100
(3)	100
(4)	100

As being apparent from the above test results, the object compound (I) of the present invention are useful as antiulcer medicines.

For therapeutic purpose, the compounds according to the present invention can be used in a form of pharmaceutical preparation containing said compound as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral or parenteral administration. The pharmaceutical preparations may be capsules, tablets, dragees, solution, suspension, emulsion, and the like. If desired, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compounds will vary depending upon the age and condition of the patient, an average single dose of about 5 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg, and 1000 mg of the compounds according to the present invention may be effective for treating ulcer. In general, amounts between 1 mg/body and about 2,000 mg/body or even more may be administered per day.

The following preparations and examples are given for the purpose of illustrating the present invention.

Preparation 1

Sodium borohydride (0.248 g) was added portionwise to a solution of 4-acetamido-2-methyl benzaldehyde (2.58 g) in methanol (26 ml) with ice-cooling. After being stirred for 3 hours, the mixture was evaporated in vacuo and the residue was washed with water and dried to give 4-acetamido-2-methylbenzyl alcohol (2.22 g).

mp : 133 to 134 ° C
 IR (Nujol) : 3275, 3225, 1660, 1610, 1540, 1500, 1005 cm⁻¹
 NMR (DMSO-d₆, δ) : 2.03 (3H, s), 2.23 (3H, s), 4.43 (2H, d, J = 5Hz), 4.90 (1H, t, J = 5Hz), 7.10-7.56 (3H, m), 9.75 (1H, br s)

Preparation 2

A mixture of 3-hydroxy-2-nitropyridine (3.08 g) and potassium carbonate (3.04 g) in N,N-dimethylformamide (31 ml) was stirred at room temperature for 15 minutes and then 2-methoxycarbonylamino-6-

methylbenzyl chloride (4.7 g) was added. After being stirred for 6 hours, the mixture was poured into water and the resulting precipitates were collected by filtration, washed with water, and air-dried to give 3-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-nitropyridine (6.35 g).

- mp : 118 to 119 °C (recrystallized from ethanol)
 5 IR (Nujol) : 3280, 1700, 1595, 1515 cm⁻¹
 NMR (CDCl₃, δ) : 2.40 (3H, s), 3.73 (3H, s), 5.23 (2H, s), 6.90-7.80 (6H, m), 8.07-8.20 (1H, m)

Preparation 3

10 The following compounds were prepared according to a similar manner to that of Preparation 2.

- (1) 3-(2-Isonicotinamido-6-methylbenzyloxy)-2-nitropyridine
 mp : 118 to 122 °C
 IR (Nujol) : 3160, 1650, 1595, 1520 cm⁻¹
 NMR (CDCl₃, δ) : 2.43 (3H, s), 5.26 (2H, s), 7.16 (1H, d, J=8Hz), 7.37 (1H, t, J=8Hz), 7.43-7.83
 15 (5H, m), 8.10-8.20 (1H, m), 8.66-8.80 (2H, m), 8.91 (1H, broad s)
- (2) 3-(2-Methyl-6-propionamidobenzyloxy)-2-nitropyridine
 mp : 134 to 135 °C
 IR (Nujol) : 3210, 1635, 1580, 1550, 1530 cm⁻¹
 NMR (CDCl₃, δ) : 1.20 (3H, t, J=7.5Hz), 2.43 (3H, s), 2.45 (2H, q, J=7.5Hz), 5.24 (2H, s), 7.08
 20 (1H, d, J=7Hz), 7.33 (1H, t, J=7Hz), 7.50-7.80 (3H, m), 8.08 (1H, broad s), 8.20 (1H, dd, J=2Hz, 4.5Hz)
- (3) 3-(2-t-Butoxycarbonylaminoacetamido-6-methylbenzyloxy)-2-nitropyridine
 mp : 156 to 158 °C
 IR (Nujol) : 3300, 1710, 1685, 1595, 1530 cm⁻¹
 25 NMR (CDCl₃, δ) : 1.30 (9H, s), 2.40 (3H, s), 3.95 (2H, d, J=6Hz), 5.20 (2H, s), 5.30 (1H, t, J=6Hz), 7.08 (1H, d, J=7.5Hz), 7.30 (1H, t, J=7.5Hz), 7.50-7.83 (3H, m), 8.17 (1H, dd, J=2Hz, 4.5Hz), 8.58 (1H, broad s)
- (4) 3-(2-Benzoyloxycarbonylamino-6-methylbenzyloxy)-2-nitropyridine
 mp : 116 to 118 °C (recrystallized from a mixture of diethyl ether and n-hexane)
 30 IR (Nujol) : 3225, 1718, 1590, 1520 cm⁻¹
 NMR (CDCl₃, δ) : 2.40 (3H, s), 5.21 (4H, s), 6.93-7.73 (12H, m), 8.06-8.20 (1H, m)
- (5) 3-(2-Isopropoxycarbonylamino-6-methylbenzyloxy)-2-nitropyridine
 mp : 106 to 107 °C (recrystallized from a mixture of diethyl ether and n-hexane)
 IR (Nujol) : 3200, 1670, 1590, 1523 cm⁻¹
 35 NMR (CDCl₃, δ) : 1.29 (6H, d, J=6Hz), 2.42 (3H, s), 5.0 (1H, septet, J=6Hz), 5.26 (2H, s), 6.93-7.76 (6H, m), 8.08-8.23 (1H, m)
- (6) 3-(4-Acetamido-2-methylbenzyloxy)-2-aminopyridine
 mp : 189 to 193 °C (recrystallized from a mixture of ethanol and n-hexane)
 IR (Nujol) : 3470, 3410, 3300, 1695, 1670, 1600, 1560, 1525 cm⁻¹
 40 NMR (DMSO-d₆, δ) : 2.03 (3H, s), 2.30 (3H, s), 5.01 (2H, s), 5.52 (2H, br s), 6.50 (1H, dd, J=5Hz, 8Hz), 7.12 (1H, broad d, J=8Hz), 7.33-7.66 (4H, m), 9.84 (1H, br s)
- (7) 3-(2-Acetoxyacetamido-6-methylbenzyloxy)-2-nitropyridine
 mp : 140 to 141 °C (recrystallized from a mixture of diethyl acetate and n-hexane)
 IR (Nujol) : 3200, 1740, 1655, 1595, 1525 cm⁻¹
 45 NMR (CDCl₃, δ) : 1.90 (3H, s), 2.40 (3H, s), 4.65 (2H, s), 5.18 (2H, s), 6.95-7.87 (5H, m), 8.11 (1H, dd, J=2Hz, 4Hz), 8.30 (1H, broad s)
- (8) 3-(2-t-Butoxycarbonylamino-6-methylbenzyloxy)-2-nitropyridine
 mp : 101-103 °C
 IR (Nujol) : 3290, 1710, 1585, 1525 cm⁻¹
 50 NMR (CDCl₃, δ) : 1.5 (9H, s), 2.4 (3H, s), 5.26 (2H, s), 6.9-7.8 (6H, m), 8.06-8.23 (1H, m)

Preparation 4

To a mixture of iron powder (2.76 g) and ammonium chloride (0.275 g) in water (19 ml) and ethanol (63
 55 ml) was added portionwise 3-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-nitropyridine (6.27 g) under reflux and then stirred for an additional 30 minutes. The hot mixture was filtered by suction and the filtrate was made alkaline with sodium bicarbonate and evaporated in vacuo. The residue was washed with water, dried, and recrystallized from ethyl acetate to give 2-amino-3-(2-methoxycarbonylamino-6-

methylbenzyloxy)pyridine.

mp : 146 to 148 °C
 IR (Nujol) : 3430, 3375, 3270, 3150, 1730, 1620, 1585, 1520, 1230, 1190 cm⁻¹
 NMR (CDCl₃, δ) : 2.37 (3H, s), 3.73 (3H, s), 4.62 (2H, broad s), 5.03 (2H, s), 6.47-6.67 (1H, m), 6.90-7.35 (4H, m), 7.50-7.73 (2H, m)

Preparation 5

The following compounds were prepared according to a similar manner to that of Preparation 4.

(1) 2-Amino-3-(2-isonicotinamido-6-methylbenzyloxy)pyridine

mp : 186 to 188 °C
 IR (Nujol) : 3475, 3235, 3125, 1655, 1620, 1520 cm⁻¹
 NMR (DMSO-d₆, δ) : 2.43 (3H, s), 5.06 (2H, s), 5.51 (2H, s), 6.46 (1H, dd, J=4.5Hz, 7.5Hz), 7.13 (1H, broad d, J=7.5Hz), 7.16-7.43 (3H, m), 7.51 (1H, dd, J=1.5Hz, 4.5Hz), 7.80-7.93 (2H, m), 8.73-8.86 (2H, m), 10.33 (1H, s)

(2) 2-Amino-3-(2-methyl-6-propionamidobenzyloxy)pyridine

mp : 161 to 162 °C
 IR (Nujol) : 3450, 3280, 3120, 1640, 1610, 1520 cm⁻¹
 NMR (CDCl₃, δ) : 1.15 (3H, t, J=8Hz), 2.35 (2H, q, J=8Hz), 2.41 (3H, s), 4.63 (2H, broad s), 5.05 (2H, s), 6.53-6.80 (1H, m), 6.96-7.87 (6H, m)

(3) 2-Amino-3-(2-t-butoxycarbonylaminoacetamido-6-methylbenzyloxy)pyridine

mp : 169 to 170 °C
 IR (Nujol) : 3480, 3435, 3360, 1703, 1685, 1615, 1200 cm⁻¹
 NMR (CDCl₃, δ) : 1.38 (9H, s), 2.40 (3H, s), 3.88 (2H, d, J=6Hz), 4.70 (2H, broad s), 5.10 (2H, s), 5.33-5.70 (1H, m), 6.47-6.83 (1H, m), 6.83-7.50 (3H, m), 7.60-7.93 (2H, m), 8.75 (1H, broad s)

(4) 2-Amino-3-(2-benzyloxycarbonylamino-6-methylbenzyloxy)pyridine

mp : 107 to 109 °C (recrystallized from diethyl ether)
 IR (Nujol) : 3460, 3350, 1700, 1615, 1585, 1540 cm⁻¹
 NMR (CDCl₃, δ) : 2.39 (3H, s), 4.63 (2H, br s), 5.06 (2H, s), 5.20 (2H, s), 6.63 (1H, dd, J=5Hz, 8Hz), 7.05 (1H, dd, J=2Hz, 8Hz), 7.16-7.50 (8H, m), 7.63 (1H, br s), 7.73 (1H, dd, J=2Hz, 5Hz)

(5) 2-Amino-3-(2-isopropoxycarbonylamino-6-methylbenzyloxy)pyridine

mp : 112 to 114 °C (recrystallized from a mixture of diethyl ether and n-hexane)
 IR (Nujol) : 3450, 3280, 1685, 1620, 1510 cm⁻¹
 NMR (CDCl₃, δ) : 1.26 (6H, d, J=7Hz), 2.37 (3H, s), 4.68 (2H, br s), 5.0 (1H, septet, J=7Hz), 5.06 (2H, s), 6.62 (1H, dd, J=5Hz, 8Hz), 6.90-7.23 (3H, m), 7.38 (1H, d, J=8Hz), 7.56-7.83 (2H, m)

(6) 3-(2-Acetoxyacetamido-6-methylbenzyloxy)-2-aminopyridine

mp : 151 to 152 °C
 IR (Nujol) : 3460, 3330, 1740, 1685, 1620, 1555 cm⁻¹
 NMR (CDCl₃, δ) : 1.73 (3H, s), 2.43 (3H, s), 4.67 (2H, s), 5.10 (2H, s), 6.57-6.87 (1H, m), 7.0-7.57 (3H, m), 7.67-8.02 (2H, m), 8.50 (1H, broad s)

(7) 2-Amino-3-(2-t-butoxycarbonylamino-6-methylbenzyloxy)pyridine

mp : 116-118 °C
 IR (Nujol) : 3475, 3425, 3275, 3125, 1725, 1620, 1595, 1580, 1510 cm⁻¹
 NMR (CDCl₃, δ) : 1.50 (9H, s), 2.38 (3H, s), 4.63 (2H, br s), 5.08 (2H, s), 6.65 (1H, dd, J=5Hz, 8Hz), 6.90-7.20 (3H, m), 7.30 (1H, t, J=8Hz), 7.56-7.86 (2H, m)

Preparation 6

A solution of 2-amino-3-(2-acetoxyacetamido-6-methylbenzyloxy)pyridine (0.63 g) and 1N sodium hydroxide solution (2 ml) in methanol (20 ml) was stirred at room temperature for 1 hour. The resulting precipitates were collected by filtration to give 2-amino-3-(2-hydroxyacetamido-6-methylbenzyloxy)pyridine.

mp : 207 to 209 °C (dec.)
 IR (Nujol) : 3440, 3350, 1675, 1625, 1540 cm⁻¹
 NMR (DMSO-d₆, δ) : 2.43 (3H, s), 4.03 (2H, s), 5.12 (2H, s), 5.50 (2H, br s), 6.43-7.73 (1H, m), 7.0-7.8 (5H, m)

Preparation 7

Acetic formic anhydride (1.85 g) was added to a solution of 2-amino-6-methylbenzyl alcohol (2.74 g) in benzene (55 ml) at room temperature. After being stirred for 2 hours, the mixture was diluted with n-hexane (10 ml) and the precipitates were collected by filtration to give 2-formamido-6-methylbenzyl alcohol (2.8 g).

mp : 99 to 100 ° C
 IR (Nujol) : 3240, 1660, 1595, 1575, 1520 cm⁻¹
 NMR (DMSO-d₆, δ) : 2.33 (3H, s), 4.48 (2H, s),

10

6.83-7.23 } (3H, m), 8.24 (s) } (1H)
 7.43-7.63 } (3H, m), 8.37 (s) } (1H)

Preparation 8

A mixture of 2-amino-6-methylbenzyl alcohol (0.274 g) and methyl isocyanate (0.11 g) in benzene (5.2 ml) was stirred at room temperature for 15 minutes. The resulting precipitates were collected by filtration and dried to give 6-methyl-2-(3-methyl ureido)benzyl alcohol (0.24 g)

mp : 158 to 160 ° C (dec.)
 IR (Nujol) : 3375, 3260, 1665, 1600, 1550, 990 cm⁻¹
 NMR (DMSO-d₆, δ) : 2.30 (3H, s), 2.62 (3H, d, J=4.5Hz), 4.47 (2H, broad d), 4.7-5.3 (1H, m), 6.47-6.80 (1H, m), 6.80 (1H, dd, J=2Hz, 8Hz), 7.05 (1H, t, J=8Hz), 7.53 (1H, dd, J=2Hz, 8Hz), 7.90 (1H, s)

25

Preparation 9

A solution of methylchloroformate (0.416 g) in methylene chloride (1 ml) was added dropwise to a solution of 2-amino-6-methylbenzyl alcohol (0.549 g) and pyridine (0.364 g) in methylene chloride (10 ml) with ice cooling. After being stirred for 1 hour, the mixture was poured into 1N hydrochloric acid and extracted with methylene chloride. The extract was washed with water, dried over magnesium sulfate, and evaporated in vacuo. The crystalline residue was washed with n-hexane and dried to give 2-methoxycarbonylamino-6-methylbenzyl alcohol (0.64 g).

mp : 111 to 113 ° C
 IR (Nujol) : 3450, 3260, 1685, 1602, 1580, 1540 cm⁻¹
 NMR (CDCl₃, δ) : 2.36 (3H, s), 2.46 (1H, t, J=6Hz), 3.73 (3H, s), 4.67 (2H, d, J=6Hz), 6.87 (1H, d, J=7.5Hz), 7.11 (1H, t, J=7.5Hz), 7.47 (1H, d, J=7.5Hz), 7.40-7.70 (1H, broad s)

Preparation 10

40

To a solution of t-butoxycarbonylaminoacetic acid (3.5 g) in methylene chloride (50 ml) was added triethylamine (2.0 g) and then ethyl chloroformate (1.9 ml) with ice-cooling. After being stirred for 1 hour, 2-amino-6-methylbenzyl alcohol (2.74 g) was added thereto and the mixture was stirred for 7 days at an ambient temperature. To the mixture was added a saturated aqueous solution of sodium hydrogen carbonate and the organic layer was separated, washed with water and dried over magnesium sulfate. The solvent was distilled off and the residue was triturated with diethyl ether to give 2-(t-butoxycarbonylaminoacetamido)-6-methylbenzyl alcohol (1.04 g).

mp : 138 to 141 ° C
 IR (Nujol) : 3410, 3270, 1705, 1645, 1595, 1575, 1240 cm⁻¹
 NMR (CDCl₃, δ) : 1.45 (9H, s), 2.35 (3H, s), 3.86 (2H, d, J=6Hz), 4.63 (2H, s), 5.55 (1H, t, J=6Hz), 6.86-7.06 (1H, m), 7.17 (1H, t, J=7.5Hz), 7.57 (1H, broad d, J=7.5Hz), 9.10 (1H, broad s)

Preparation 11

55

A solution of potassium cyanate (1.62 g) in water (5 ml) was added dropwise to a mixture of 2-amino-6-methylbenzyl alcohol (1.37 g), water (5 ml), and acetic acid (6 ml) at room temperature. After being stirred for 2.5 hours, the resulting precipitates were collected by filtration, washed with water, and dried to give 6-

methyl-2-ureidobenzyl alcohol (1.33 g).

mp : 161 to 163 °C (dec.) (recrystallized from ethanol)
 IR (Nujol) : 3350, 3270, 1655, 1590, 1530, 1000 cm^{-1}
 NMR (DMSO- d_6 , δ) : 2.32 (3H, s), 4.45 (2H, d, J=5Hz), 4.93 (1H, d, J=5Hz), 6.08 (2H, broad s), 6.82 (1H, d, J=8Hz), 7.05 (1H, t, J=8Hz), 7.55 (1H, d, J=8Hz), 7.93 (1H, s)

Preparation 12

The following compounds were prepared according to similar manners to those of Preparations 7 to 11.

- 10 (1) 2-Benzoyloxycarbonylamino-6-methylbenzyl alcohol
 mp : 91 to 93 °C
 IR (Nujol) : 3430, 3375, 1700, 1600, 1585, 1525 cm^{-1}
 NMR (CDCl_3 , δ) : 2.33 (3H, s), 2.23-2.73 (1H, br s), 4.66 (2H, s), 5.16 (2H, s), 6.92 (1H, d, J=8Hz), 7.16 (1H, t, J=8Hz), 7.26-7.50 (5H, m), 7.57 (1H, d, J=8Hz), 7.80 (1H, br s)
- 15 (2) 2-Isopropoxycarbonylamino-6-methylbenzyl alcohol
 mp : 59 to 61 °C (recrystallized from n-hexane)
 IR (Nujol) : 3420, 3325, 1700, 1600, 1590, 1520 cm^{-1}
 NMR (CDCl_3 , δ) : 1.28 (6H, d, J=6Hz), 2.36 (3H, s), 2.70 (1H, br s), 4.69 (2H, s), 5.00 (1H, septet, J=6Hz), 6.96 (1H, d, J=7Hz), 7.20 (1H, t, J=7Hz), 7.50-7.66 (2H, m)
- 20 (3) 2-Ethoxycarbonylamino-6-methylbenzyl alcohol
 mp : 58 to 59 °C (recrystallized from n-hexane)
 IR (Nujol) : 3415, 3320, 1695, 1685, 1620, 1600 cm^{-1}
 NMR (CDCl_3 , δ) : 1.30 (3H, t, J=7Hz), 2.36 (3H, s), 2.30-2.70 (1H, br s), 4.21 (2H, q, J=7Hz), 4.70 (2H, s), 6.93 (1H, br dd, J=2Hz, 8Hz), 7.19 (1H, t, J=8Hz), 7.55 (1H, br dd, J=2Hz, 8Hz), 7.50-7.80 (1H, br s)
- 25 (4) 2-Methanesulfonylamino-6-methylbenzyl alcohol
 mp : 79 to 81 °C (recrystallized from cyclohexane)
 IR (Nujol) : 3380, 3225, 3050, 1580, 1515, 1140, 1095, 1070 cm^{-1}
 NMR (CDCl_3 , δ) : 2.39 (3H, s), 2.87 (1H, br t, J=5Hz), 3.01 (3H, s), 4.82 (2H, br d, J=5Hz), 6.93-6.40 (3H, m), 7.69 (1H, br s)
- 30 (5) 3-Acetamido-2-methylbenzyl alcohol
 mp : 117 to 118 °C
 IR (Nujol) : 3250, 1645, 1600, 1535, 1100 cm^{-1}
 NMR (DMSO- d_6 , δ) : 2.02 (3H, s), 2.06 (3H, s), 4.50 (2H, d, J=5Hz), 5.02 (1H, t, J=5Hz), 7.00-7.30 (3H, m), 9.29 (1H, br s)
- 35 (6) 2-Acetoxyacetamido-6-methylbenzyl alcohol
 mp : 108 to 110 °C (recrystallized from ethyl acetate)
 IR (Nujol) : 3280, 1760, 1660, 1605, 1580, 1530, 1210 cm^{-1}
 NMR (CDCl_3 , δ) : 2.23 (3H, s), 2.40 (3H, s), 2.60 (1H, t, J=7.5Hz), 4.70 (2H, s), 4.73 (2H, d, J=7.5Hz), 6.87-7.43 (2H, m), 7.70-7.93 (1H, m), 9.23 (1H, br s)
- 40 (7) 2-t-Butoxycarbonylamino-6-methylbenzyl alcohol
 mp : 96 to 98 °C
 IR (Nujol) : 3450, 3320, 1695, 1600, 1580, 1520 cm^{-1}
 NMR (CDCl_3 , δ) : 1.50 (9H, s), 2.40 (2H, s), 4.73 (2H, d, J=6Hz), 6.80-7.63 (4H, m)
- 45 (8) 2-Acetamido-6-methylbenzyl alcohol
 mp : 118 to 119 °C
 IR (Nujol) : 3360, 3280, 1645, 1600, 1530 cm^{-1}
 NMR (DMSO- d_6 , δ) : 2.07 (3H, s), 2.37 (3H, s), 4.50 (2H, s), 6.87-7.47 (3H, m), 9.33 (1H, br s)
- 50 (9) 2-Isonicotinamido-6-methylbenzyl alcohol
 mp : 133 to 135 °C (recrystallized from benzene)
 IR (Nujol) : 3260, 1630, 1600, 1578, 1520, 1005 cm^{-1}
 NMR (CDCl_3 , δ) : 2.30 (3H, s), 4.05 (1H, broad s), 4.83 (2H, s), 6.96 (1H, d, J=8Hz), 7.21 (1H, t, J=8Hz), 7.70-7.86 (2H, m), 8.01 (1H, d, J=8Hz), 8.53-8.80 (2H, m), 10.21 (1H, s)
- 55 (10) 2-Methyl-6-propionamidobenzyl alcohol
 mp : 75 to 76 °C
 IR (Nujol) : 3275, 1650, 1600, 1585, 1520, 1005 cm^{-1}
 NMR (CDCl_3 , δ) : 1.20 (3H, t, J=7.5Hz), 2.35 (3H, s), 2.37 (2H, g, J=7.5Hz), 3.16 (1H, broad s),

4.60 (2H, s), 6.98 (1H, broad d, $J=7.5\text{Hz}$), 7.16 (1H, t, $J=7.5\text{Hz}$), 7.52 (1H, broad d, $J=7.5\text{Hz}$), 8.52 (1H, broad s)

Preparation 13

5

A mixture of 6-methyl-2-ureidobenzyl alcohol (1 g) and thionyl chloride (0.66 g) in methylene chloride (20 ml) was stirred for 2 hours at room temperature and evaporated in vacuo. The residue was washed with water and dried in a desiccator to give 6-methyl-2-ureidobenzyl chloride (0.66 g).

IR (Nujol) : 3250, 1650, 1540 cm^{-1}

10 NMR (DMSO-d_6 , δ) : 4.83 (2H, s)

Preparation 14

The following compounds were prepared according to a similar manner to that of Preparation 13.

15

(1) 2-Acetoxyacetamido-6-methylbenzyl chloride

mp : 113 to 115 °C

IR (Nujol) : 3260, 1740, 1660, 1600, 1540, 1220 cm^{-1}

NMR (CDCl_3 , δ) : 2.27 (3H, s), 2.45 (3H, s), 4.67 (2H, s), 4.77 (2H, s), 7.10 (1H, d, $J=8\text{Hz}$), 7.30 (1H, t, $J=8\text{Hz}$), 7.77 (1H, d, $J=8\text{Hz}$), 8.27 (1H, br s)

20

(2) 2-Isonicotinamido-6-methylbenzyl chloride mono hydrochloride

mp : 247 °C (dec.)

IR (Nujol) : 3240, 3050, 1650, 1590, 1530 cm^{-1}

NMR (DMSO-d_6 , δ) : 2.46 (3H, s), 4.93 (2H, s), 7.10-7.46 (3H, m), 8.40-8.63 (2H, m), 9.0-9.26 (2H, m), 10.57 (1H, broad s), 10.90 (1H, broad s)

25

(3) 2-Methyl-6-propionamidobenzyl chloride

mp : 105 to 109 °C (dec.)

IR (Nujol) : 3260, 1650, 1585, 1520 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.10 (3H, t, $J=7\text{Hz}$), 2.16-2.60 (3H, g, $J=7\text{Hz}$), 2.39 (3H, s), 4.80 (2H, s), 7.0-7.43 (3H, m), 9.53 (1H, s)

30

(4) 2-t-Butoxycarbonylaminoacetamido-6-methylbenzyl chloride

mp : 70 to 73 °C

IR (Nujol) : 3350, 1695, 1680, 1580, 1495 cm^{-1}

NMR (CDCl_3 , δ) : 1.47 (9H, s), 2.40 (3H, s), 3.95 (2H, d, $J=6\text{Hz}$), 4.63 (2H, s), 5.33 (1H, t, $J=6\text{Hz}$), 7.03 (1H, d, $J=8\text{Hz}$), 7.23 (1H, t, $J=8\text{Hz}$), 7.63 (1H, d, $J=8\text{Hz}$), 8.33 (1H, broad s)

35

(5) 2-Formamido-6-methylbenzyl chloride

mp : 126 to 129 °C

IR (Nujol) : 3200, 1650, 1525, 1280 cm^{-1}

NMR (CDCl_3 , δ) : 2.43 (3H, s), 4.64 (2H, s), 6.90-7.80 (4H, m), 8.40, 8.52 (1H, each s)

40

MASS : M^+ 183

(6) 2-Benzyloxycarbonylamino-6-methylbenzyl chloride

mp : 114 to 115 °C

IR (Nujol) : 3290, 1685, 1600, 1590, 1525 cm^{-1}

NMR (CDCl_3 , δ) : 2.41 (3H, s), 4.65 (2H, s), 5.22 (2H, s), 6.83 (1H, br s), 6.99 (1H, br dd, $J=2\text{Hz}$, 8Hz), 7.17 (1H, d, $J=8\text{Hz}$), 7.39 (5H, s), 7.62 (1H, br dd, $J=2\text{Hz}$, 8Hz)

45

(7) 2-Isopropoxycarbonylamino-6-methylbenzyl chloride

mp : 141 to 146 °C

IR (Nujol) : 3275, 1685, 1600, 1585, 1525 cm^{-1}

NMR (DMSO-d_6 , δ) : 1.23 (6H, d, $J=6\text{Hz}$), 2.39 (3H, s), 4.83 (2H, s), 4.87 (1H, septet, $J=6\text{Hz}$), 6.93-7.45 (3H, m), 8.89 (1H, s)

50

(8) 2-Ethoxycarbonylamino-6-methylbenzyl chloride

mp : 112 to 113 °C

IR (Nujol) : 3260, 1680, 1590, 1580, 1520 cm^{-1}

NMR (CDCl_3 , δ) : 1.31 (3H, t, $J=7\text{Hz}$), 2.41 (3H, s), 4.25 (2H, q, $J=7\text{Hz}$), 4.66 (2H, s), 6.75 (1H, br s), 7.01 (1H, d, $J=8\text{Hz}$), 7.25 (1H, t, $J=8\text{Hz}$), 7.62 (1H, d, $J=8\text{Hz}$)

55

(9) 2-Methanesulfonylamino-6-methylbenzyl chloride

mp : 156 to 158 °C

IR (Nujol) : 3230, 1590, 1320, 1140 cm^{-1}

- NMR (CDCl₃, δ) : 2.46 (3H, s), 3.10 (3H, s), 4.76 (2H, s), 6.69 (1H, br s), 7.05-7.50 (3H, m)
- (10) 3-Acetamido-2-methylbenzyl chloride
- IR (Nujol) : 3260, 1645, 1590, 1525 cm⁻¹
- NMR (DMSO-d₆, δ) : 2.05 (3H, s), 2.22 (3H, s), 4.80 (2H, s), 7.05-7.50 (3H, m), 9.37 (1H, br s)
- 5 (11) 4-Acetamido-2-methylbenzyl chloride
- mp : 143 to 145 °C
- IR (Nujol) : 3310, 3190, 3125, 1665, 1610, 1540 cm⁻¹
- NMR (DMSO-d₆, δ) : 2.02 (3H, s), 2.32 (3H, s), 4.69 (2H, s), 7.10-7.43 (3H, m), 9.83 (1H, br s)
- (12) 6-Methyl-2-(3-methylureido)benzyl chloride
- 10 mp : 172 to 175 °C
- IR (Nujol) : 3325, 3260, 1620, 1565, 1260 cm⁻¹
- NMR (CDCl₃, δ) : 2.43 (3H, s), 3.80 (3H, s), 4.67 (2H, s), 6.50-7.75 (5H, m)
- (13) 2-Methoxycarbonylamino-6-methylbenzyl chloride
- mp : 125 to 127 °C
- 15 IR (Nujol) : 3275, 1680, 1595, 1580, 1520 cm⁻¹
- NMR (CDCl₃, δ) : 2.42 (3H, s), 3.78 (3H, s), 4.65 (2H, s), 6.55-7.00 (1H, broad s), 7.00 (1H, dd, J=2Hz, 7.5Hz), 7.25 (1H, t, J=7.5Hz), 7.60 (1H, dd, J=7.5Hz)
- (14) 5-Acetamido-2-methylbenzyl chloride
- mp : 76 to 79 °C
- 20 IR (Nujol) : 3220, 1650, 1590, 1320, 1260 cm⁻¹
- NMR (CDCl₃, δ) : 2.23 (3H, s), 2.37 (3H, s), 4.55 (2H, s), 7.00-7.60 (3H, m), 8.20-8.70 (1H, broad s)
- (15) 2-t-Butoxycarbonylamino-6-methylbenzyl chloride
- mp : 75 to 76 °C
- IR (Nujol) : 3355, 1685, 1600, 1582, 1510 cm⁻¹
- 25 NMR (CDCl₃, δ) : 1.52 (9H, s), 2.42 (3H, s), 4.67 (2H, s), 6.60 (1H, broad s), 7.0 (1H, d, J=7.5Hz), 7.40 (1H, t, J=7.5Hz), 7.80 (1H, d, J=7.5Hz)
- (16) 2-Acetamido-6-methylbenzyl chloride
- mp : 182 to 186 °C (dec.)
- IR (Nujol) : 3360, 1650, 1600, 1530 cm⁻¹
- 30 NMR (CDCl₃, δ) : 2.07 (3H, s), 2.40 (3H, s), 4.80 (2H, s), 7.00-7.40 (3H, m), 9.53 (1H, br s)

Preparation 15

A mixture of 2,6-dinitrobenzyl acetate (0.56 g), platonic oxide (73 mg), acetic acid (6 ml) and acetic anhydride (6 ml) was stirred in hydrogen gas at room temperature until the theoretical amount of hydrogen gas had been absorbed. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The resultant residue was subjected to column chromatography on silica gel (18 g) and eluted with a mixture of chloroform and methanol (100:3) to give 2,6-di(acetamido)benzyl acetate (0.45 g).

- mp : 222 to 223 °C
- 40 IR (Nujol) : 3260, 1725, 1650, 1220 cm⁻¹
- NMR (DMSO-d₆, δ) : 1.97 (3H, s), 2.03 (6H, s), 5.03 (2H, s), 7.13-7.32 (3H, m), 9.40 (2H, br s)

Preparation 16

45 To a solution of 2,6-di(acetamido)benzyl acetate (0.97 g) in methanol (70 ml) was added an aqueous solution (1.8 ml) of potassium carbonate (608 mg) and the mixture was stirred at room temperature for 1 hour. After methanol was evaporated under reduced pressure, the resultant residue was subjected to column chromatography on silica gel (18 g) and eluted with a mixture of chloroform and methanol (20:1) to give 2,6-di(acetamido)benzyl alcohol (0.67 g).

- 50 mp : 161 to 162 °C
- IR (Nujol) : 3270, 1650, 1380 cm⁻¹
- NMR (DMSO-d₆, δ) : 2.05 (6H, s), 4.50 (2H, d, J=5Hz), 5.30 (1H, t, J=5Hz), 7.17-7.53 (3H, m), 9.47 (2H, br s)

Preparation 17

A solution of 2-amino-3-methoxymethoxypyridine (7.5 g) and 3-mesyloxy-5-hexyn-2-one (10.18 g) in ethanol (150 ml) was refluxed for 46.5 hours and then evaporated in vacuo. To the residue was added 20%

sulfuric acid (75 ml) and the mixture was stirred for 5 hours at room temperature. The mixture was made alkaline with sodium bicarbonate and extracted with chloroform. The extract was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (30 g) with chloroform and then a mixture of chloroform and methanol (30:1 to 20:1) as eluents.

- 5 The eluates were evaporated in vacuo and the residue was recrystallized from a mixture of ethyl acetate and n-hexane to give 8-hydroxy-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine (1.93 g).

mp : 175 to 177 ° C

NMR (CDCl₃, δ) : 2.03 (1H, t, J = 3Hz), 2.45 (3H, s), 3.73 (2H, d, J = 3Hz), 6.70-6.90 (2H, m), 7.57-7.76 (1H, m), 11.29 (1H, s)

10

Example 1

A mixture of 8-hydroxy-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine (0.571 g) and potassium carbonate (0.424 g) in N,N-dimethylformamide (11.5 ml) was stirred at room temperature for 20 minutes under a nitrogen atmosphere and then 6-methyl-2-ureidobenzyl chloride (0.6 g) was added. After being stirred for 2.5 hours. The mixture was poured into water and the resulting precipitates were collected by filtration. The crude product was purified by column chromatography on silica gel (25 g) with a mixture of chloroform and methanol (100:1 to 100:4) as eluents to give 2-methyl-8-(6-methyl-2-ureidobenzoyloxy)-3-(2-propynyl)imidazo[1,2-a]pyridine (0.13 g).

20 mp : 197 to 199 ° C (dec.)

IR (Nujol) : 3380, 3270, 3240, 3170, 1660, 1590, 1540, 1090 cm⁻¹

NMR (DMSO-d₆, δ) : 2.30 (3H, s), 2.35 (3H, s), 2.97 (1H, t, J = 3Hz), 3.95 (2H, d, J = 3Hz), 5.23 (2H, s), 6.10 (2H, s), 6.70-7.43 (4H, m), 7.60-8.10 (2H, m), 8.20 (1H, s)

25 Example 2

The following compounds were prepared according to a similar manner to that of Example 1.

(1) 8-(2-Formamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 189 to 190 ° C (recrystallized from ethanol)

30 IR (Nujol) : 3200, 1685, 1605, 1585, 1540, 1280 cm⁻¹

NMR (CDCl₃, δ) : 2.08 (1H, t, J = 3Hz), 2.45, 2.50, 2.52, 2.57 (6H, each s), 3.75 (2H, d, J = 3Hz), 5.28, 5.33 (2H, each s), 6.55-7.30, 7.65-8.10 (6H, m), 8.40-8.63 (1H, m), 10.70-11.20 (1H, broad m)

MASS : M⁺ 333

35 (2) 8-(2-Ethoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 175 to 177 ° C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3280, 1710, 1540 cm⁻¹

40 NMR (CDCl₃, δ) : 1.29 (3H, t, J = 6Hz), 2.06 (1H, t, J = 3Hz), 2.47 (3H, s), 2.50 (3H, s), 3.76 (2H, d, J = 3Hz), 4.20 (2H, q, J = 6Hz), 5.38 (2H, s), 6.60-6.80 (2H, m), 6.92 (1H, d, J = 7.5Hz), 7.21 (1H, t, J = 7.5Hz), 7.63 (1H, d, J = 7.5Hz), 7.70-7.83 (1H, m), 8.89 (1H, br s)

(3) 8-(2-Methanesulfonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 135 to 136 ° C (recrystallized from a mixture of ethyl acetate and n-hexane)

45 IR (Nujol) : 3275, 1540, 1323, 1145 cm⁻¹

NMR (CDCl₃, δ) : 2.06 (1H, t, J = 3Hz), 2.53 (6H, s), 2.93 (3H, s), 3.76 (2H, d, J = 3Hz), 5.47 (2H, s), 6.62-6.90 (2H, m), 6.96-7.33 (1H, br s), 7.03 (1H, br d, J = 7Hz), 7.22 (1H, t, J = 7Hz), 7.52 (1H, dd, J = 7Hz), 7.83 (1H, dd, J = 1.5Hz, 6Hz)

50

Analysis Calcd. for C ₂₀ H ₂₁ N ₃ O ₃ S :			
Found :	C 62.64, C 62.72,	H 5.52, H 5.57,	N 10.96 N 10.16

55 (4) 8-(3-Acetamido-2-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 207 to 208 ° C (recrystallized from ethanol and diisopropyl ether)

IR (Nujol) : 3200, 1635, 1540 cm⁻¹

NMR (DMSO-d₆, δ) : 2.03 (3H, s), 2.17 (3H, s), 2.30 (3H, s), 2.90 (1H, t, J = 3Hz), 3.86 (2H, d, J = 3Hz), 5.21 (2H, s), 6.63-6.86 (2H, m), 6.96-7.36 (3H, m), 7.80 (1H, dd,

J = 3Hz, 5Hz), 9.26 (1H, s)

Analysis Calcd. for C ₂₁ H ₂₁ N ₃ O ₂ :			
Found :	C 72.60, C 72.76,	H 6.09, H 5.83,	N 12.10 N 12.17

(5) 2-Methyl-8-[6-methyl-2-(3-methylureido)benzyloxy]-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 214 to 215 ° C (dec.) (recrystallized from ethanol)
 IR (Nujol) : 3400, 3290, 1695, 1605 cm⁻¹
 NMR (DMSO-d₆, δ) : 2.30 (3H, s), 2.31 (3H, s), 2.62 (3H, d, J=5Hz), 2.93 (1H, t, J=3Hz), 3.89 - (2H, d, J=3Hz), 5.13 (2H, s), 6.45 (1H, q, J=5Hz), 6.70-6.93 (3H, m), 7.14 (1H, t, J=7.5Hz), 7.57 (1H, broad d, J=7.5Hz), 7.85 (1H, t, J=4.5Hz), 8.03 (1H, s)

(6) 8-(5-Acetamido-2-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 235 to 237 ° C (dec.) (recrystallized from ethanol)
 IR (Nujol) : 3270, 1670, 1595, 1535, 1490 cm⁻¹
 NMR (DMSO-d₆, δ) : 2.00 (3H, s), 2.28 (3H, s), 2.30 (3H, s), 2.90 (1H, t, J=3Hz), 3.87 (2H, d, J=3Hz), 5.16 (2H, s), 6.57-6.88 (2H, m), 7.06 (1H, d, J=9Hz), 7.35-7.56 (2H, m), 7.80 (1H, dd, J=2Hz, 6Hz), 9.78 (1H, s)

(7) 8-(2-t-Butoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

IR (CHCl₃) : 3400, 3300, 1710, 1580, 1535, 1370, 1270, 1150 cm⁻¹
 NMR(CDCl₃, δ) : 1.47 (9H, s), 2.05 (1H, t, J=3Hz), 2.42 (3H, s), 2.47 (3H, s), 3.75 (2H, d, J=3Hz), 5.35 (2H, s), 6.55-6.70 (2H, m), 6.88 (1H, d, J=7.5Hz), 7.15 (1H, t, J=7.5Hz), 7.51 (1H, d, J=7.5Hz), 7.71 (1H, dd, J=3Hz, 5Hz), 7.98 (1H, broad s)

(8) 8-(2-Acetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 194 to 195 ° C (recrystallized from a mixture of ethanol and diisopropyl ether)
 IR (Nujol) : 3340, 3270, 1683, 1603, 1585, 1280 cm⁻¹
 NMR (CDCl₃, δ) : 2.07 (1H, t, J=3Hz), 2.17 (3H, s), 2.43 (6H, s), 3.76 (2H, d, J=3Hz), 5.30 (2H, s), 6.63-6.73 (2H, m), 6.90 (1H, br d, J=7.5Hz), 7.17 (1H, t, J=7.5Hz), 7.60-7.83 (2H, m), 9.07 (1H, br s)

Analysis Calcd. for C ₂₁ H ₂₁ N ₃ O ₂ :			
Found :	C 72.60, C 73.10,	H 6.09, H 6.21,	N 12.09 N 11.72

40 Example 3

A mixture of 2-amino-3-(2-methoxycarbonylamino-6-methylbenzyloxy)pyridine (4.22 g) and 3-mesyloxy-5-hexyn-2-one (2.74 g) in ethanol (42 ml) was refluxed for 62 hours and then evaporated in vacuo. To the residue was added an aqueous solution of sodium bicarbonate and the insoluble material was collected by filtration. The crude product was purified by column chromatography on silica gel (150 g) with methylene chloride and then a mixture of methylene chloride and acetonitrile (10:1) as eluents to afford a solid, which was recrystallized from a mixture of ethyl acetate and cyclohexane to give 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine.

mp : 179 to 180 ° C

Analysis Calcd. for C ₂₁ H ₂₁ N ₃ O ₃ :			
Found :	C 69.40, C 69.79,	H 5.82, H 5.76,	N 11.56 N 11.68

Example 4

The following compounds were prepared according to a similar manner to that of Example 3.

(1) 8-(2-Isonicotinamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 174 to 175 °C (recrystallized from ethyl acetate and n-hexane)
 IR (Nujol) : 3375, 3245, 1680, 1600, 1540, 1520 cm⁻¹
 NMR (CDCl₃, δ) : 2.10 (1H, t, J=3Hz), 2.34 (3H, s), 2.49 (3H, s), 3.76 (2H, d, J=3Hz), 5.45 (2H, s), 6.63-6.86 (2H, m), 7.07 (1H, d, J=8Hz), 7.33 (1H, t, J=8Hz), 7.75-8.00 (4H, m), 8.56-8.70 (2H, m), 9.90 (1H, broad s)

Analysis Calcd. for C₂₅H₂₂N₄O₂ :

	C 73.15,	H 5.40,	N 13.65
Found :	C 74.48,	H 5.38,	N 13.70

(2) 2-Methyl-8-(2-methyl-6-propionamidobenzyloxy)-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 164 to 165 °C (recrystallized from ethyl acetate)
 IR (Nujol) : 3310, 1690, 1600, 1585, 1540 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.05 (3H, t, J=7.5Hz), 2.31 (3H, s), 2.40 (3H, s), 2.20-2.56 (2H, 4, J=7.5Hz), 2.94 (1H, t, J=3Hz), 3.91 (2H, d, J=3Hz), 5.23 (2H, s), 6.73-7.30 (2H, m), 7.03-7.50 (3H, m), 7.95 (1H, dd, J=3.6Hz), 9.60 (1H, s)

Analysis Calcd. for C₂₂H₂₃N₃O₂ :

	C 73.11,	H 6.41,	N 11.63
Found :	C 73.14,	H 6.37,	N 14.49

(3) 8-(2-t-Butoxycarbonylaminoacetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

NMR (CDCl₃, δ) : 1.30 (9H, s), 2.08 (1H, t, J=3Hz), 2.47 (6H, s), 3.78 (2H, d, J=3Hz), 4.03 (2H, d, J=6Hz), 5.42 (2H, s), 6.70-7.40 (5H, m), 7.77-8.10 (2H, m), 9.67 (1H, broad s)

(4) 8-(2-Benzyloxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 160 to 161 °C (recrystallized from a mixture of ethyl acetate and diisopropyl ether)
 IR (Nujol) : 3290, 1705, 1540 cm⁻¹
 NMR (CDCl₃) : 2.06 (1H, t, J=3Hz), 2.33 (3H, s), 2.47 (3H, s), 3.74 (2H, d, J=3Hz), 5.20 (2H, s), 5.40 (2H, s), 6.63-6.86 (2H, m), 6.98 (1H, d, J=7Hz), 7.23-7.46 (6H, m), 7.66-7.93 (2H, m), 9.22 (1H, s)

Analysis Calcd. for C₂₇H₂₅N₃O₃ :

	C 73.79,	H 5.73,	N 9.56
Found :	C 73.41,	H 5.61,	N 9.61

(5) 8-(2-Isopropoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 119 to 120 °C (recrystallized from a mixture of diisopropyl ether and n-hexane)
 IR (Nujol) : 3280, 1705, 1540 cm⁻¹
 NMR (CDCl₃, δ) : 1.26 (6H, d, J=7Hz), 2.07 (1H, t, J=3Hz), 2.47 (3H, s), 2.52 (3H, s), 3.78 (2H, d, J=3Hz), 5.03 (1H, septet, J=7Hz), 5.43 (2H, s), 6.75 (2H, d, J=4Hz), 6.99 (1H, d, J=8Hz), 7.26 (1H, t, J=8Hz), 7.69 (1H, d, J=8Hz), 7.83 (1H, t, J=4Hz), 8.63 (1H, s)

Analysis Calcd. for C₂₃H₂₅N₃O₃ :

	C 70.57,	H 6.44,	N 10.78
Found :	C 70.60,	H 6.43,	N 10.48

(6) 8-(4-Acetamido-2-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 189 to 191 °C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3250, 1680, 1590, 1540 cm^{-1}
 NMR (CDCl_3 , δ) : 1.96 (3H, s), 2.06 (1H, t, $J=3\text{Hz}$), 2.26 (3H, s), 2.40 (3H, s), 3.76 (2H, d, $J=3\text{Hz}$),
 5.10 (1H, s), 6.55 (1H, d, $J=7\text{Hz}$), 6.75 (1H, t, $J=7\text{Hz}$), 7.13 (1H, d, $J=9\text{Hz}$),
 7.29 (1H, dd, $J=2\text{Hz}$, 9Hz), 7.45 (1H, d, $J=2\text{Hz}$), 7.73 (1H, d, $J=7\text{Hz}$), 9.41 (1H,
 br s)

Analysis Calcd. for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_2$:			
	C 72.60,	H 6.09,	N 12.10
Found :	C 72.45,	H 6.01,	N 11.80

(7) 8-(2-Hydroxyacetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 220 to 222 °C (dec.)

IR (Nujol) : 3320, 3190, 1680, 1520, 1280 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 2.33 (3H, s), 2.47 (3H, s), 2.95 (1H, t, $J=3\text{Hz}$), 3.93 (2H, d, $J=3\text{Hz}$), 4.02 (2H,
 s), 5.38 (2H, s), 6.80-7.63 (4H, m), 7.63-8.03 (2H, m), 9.67 (1H, br s)

(8) 8-(2-Acetoxyacetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 159 to 160 °C

IR (Nujol) : 3390, 3275, 1740, 1685, 1600, 1525, 1270, 1220 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.97 (3H, s), 2.30 (3H, s), 2.40 (3H, s), 2.93 (1H, t, $J=3\text{Hz}$), 3.92 (2H, d,
 $J=3\text{Hz}$), 4.67 (2H, s), 5.23 (2H, s), 6.77-7.50 (5H, m), 7.83-8.03 (1H, m), 9.73
 (1H, br s)

Example 5

A mixture of dimethylformamide (277 mg) and phosphorus oxychloride (0.35 ml) was warmed for 1 hour
 at 40 °C. After cooling, dry methylene chloride (4 ml) was added thereto. Pyruvic acid (303 mg) was added
 thereto with stirring at -20 °C and the mixture was stirred for 1 hour at the same temperature to produce an
 activated acid solution. On the other hand, 8-(2-amino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo-
 [1,2-a]pyridine (0.7 g) was dissolved in a solution of bis(trimethylsilyl)acetamide (1.2 g) in dry methylene
 chloride (10 ml). To the solution was at a time added the above obtained activated acid solution at -30 °C
 and the mixture was stirred for 30 minutes at the same temperature. To the reaction mixture was added a
 saturated aqueous solution of sodium hydrogen carbonate and the organic layer was separated, washed
 with water and dried over magnesium sulfate.

The solvent was distilled off, and the residue was subjected to column chromatography on silica gel (20
 g) and eluted with a mixture of chloroform and methanol (100:1) to give 2-methyl-3-(2-propynyl)-8-(2-
 pyruvamido-6-methylbenzyloxy)imidazo[1,2-a]pyridine (419 mg).

mp : 158 to 160 °C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3330, 3260, 1725, 1690, 1600, 1545 cm^{-1}

NMR (CDCl_3 , δ) : 2.08 (1H, t, $J=3\text{Hz}$), 2.43 (6H, s), 2.48 (3H, s), 3.78 (2H, d, $J=3\text{Hz}$), 5.38 (2H, s),
 6.65-6.92 (2H, m), 7.07 (1H, d, $J=7.5\text{Hz}$), 7.32 (1H, t, $J=7.5\text{Hz}$), 7.75-7.95 (2H, m),
 9.67 (1H, broad s)

Example 6

The following compounds were prepared according to a similar manner to that of Example 5.

(1) 8-(2-n-Butyramido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 158 to 160 °C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3275, 1680, 1600, 1583, 1535 cm^{-1}

NMR (CDCl_3 , δ) : 0.90 (3H, t, $J=7.5\text{Hz}$), 1.69 (2H, sextet, $J=7.5\text{Hz}$), 2.08 (1H, t, $J=3\text{Hz}$), 2.44 (2H,
 t, $J=7.5\text{Hz}$), 2.45 (6H, s), 3.79 (2H, d, $J=3\text{Hz}$), 5.35 (2H, s), 6.65-6.90 (2H, m),
 7.0 (1H, broad d, $J=7.5\text{Hz}$), 7.25 (1H, t, $J=7.5\text{Hz}$), 7.71-7.93 (2H, m), 9.0 (1H,
 broad s)

(2) 2-Methyl-8-(2-methoxalylamino-6-methylbenzyloxy)-3-(2-propynyl)imidazo[1,2-a]pyridine

mp : 140 to 141 °C (recrystallized from ethyl acetate and n-hexane)

IR (Nujol) : 3300, 1738, 1680, 1605, 1585, 1540 cm^{-1}

NMR (CDCl_3 , δ) : 2.06 (1H, t, $J=3\text{Hz}$), 2.43 (6H, s), 3.70-3.83 (2H, t, $J=3\text{Hz}$), 3.75 (3H, s), 5.40
 (2H, s), 6.70-6.90 (2H, m), 7.06 (1H, d, $J=8\text{Hz}$), 7.30 (1H, t, $J=8\text{Hz}$), 7.75-7.93

(2H, m), 9.95 (1H, br s)

Analysis Calcd. for $C_{22}H_{21}N_3O_4$:			
	C 67.51,	H 5.41,	N 10.74
Found :	C 66.97,	H 5.18,	N 10.84

Example 7

To a solution of 8-(2-amino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine (0.4 g) in a mixture of triethylamine (189.2 mg) and methylene chloride (9 ml) was added dropwise sulfamoyl chloride (216 mg) with ice-cooling. After being stirred for 2 hours at ambient temperature, the reaction mixture was diluted with a mixture of chloroform and methanol (95:5). The resultant organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, and then with water. The organic layer was dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The crystalline residue was recrystallized from ethanol to give 2-methyl-3-(2-propynyl)-8-(2-sulfamido-6-methylbenzyloxy)imidazo[1,2-a]pyridine.

mp : 138 to 140 °C
 IR (Nujol) : 3400, 3310, 3270, 1570, 1545 cm^{-1}
 NMR (DMSO- d_6 , δ) : 2.33 (3H, s), 2.43 (3H, s), 2.93 (1H, t, J=3Hz), 3.93 (2H, d, J=3Hz), 5.38 (2H, s), 6.83-7.50 (5H, m), 7.10 (2H, s), 7.86-8.06 (1H, m), 9.06 (1H, broad s)

Analysis Calcd. for $C_{19}H_{20}N_4O_3S$:			
	C 59.36,	H 5.24,	N 14.57
Found :	C 59.96,	H 5.30,	N 14.07

Example 8

To a solution of 2-methyl-3-(2-propynyl)-8-(2-pyruvamido-6-methylbenzyloxy)imidazo[1,2-a]pyridine (287 mg) in the mixture of acetic acid (0.13 ml) and ethanol (3 ml), sodium cyanoborohydride (72 mg) was added portionwise for 2.5 hours at 5 °C. The mixture was poured into a saturated aqueous solution of sodium hydrogen carbonate and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (10 g) and eluted with a mixture of chloroform and methanol (100:1) to give 8-(2-lactamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine (138 mg).

mp : 186 to 188 °C (recrystallized from a mixture of ethyl acetate and n-hexane)
 IR (Nujol) : 3320, 3270, 1675, 1540, 1275, 1080 cm^{-1}
 NMR (CDCl₃, δ) : 1.53 (3H, d, J=7Hz), 2.04 (1H, t, J=3Hz), 2.42 (3H, s), 2.50 (3H, s), 3.71 (2H, d, J=3Hz), 4.29 (1H, d, J=7Hz), 5.57 (2H, s), 6.43-6.80 (2H, m), 6.90 (1H, broad d, J=8Hz), 7.17 (1H, broad t, J=8Hz), 7.68 (1H, broad d, J=7.5Hz), 8.25 (1H, broad d, J=8Hz), 10.28 (1H, broad s)

Example 9

To a solution of 8-(2-t-butoxycarbonylaminoacetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine (435 mg) in ethanol (2 ml) was added 25% ethanolic hydrogen chloride (0.53 ml) with ice-cooling. After being stirred for 3 hours with ice-cooling, the solvent was evaporated under reduced pressure. To the residue was added a saturated aqueous solution of sodium hydrogen carbonate and the aqueous layer was extracted with chloroform. The extract was washed with a water and dried over magnesium sulfate. The solvent was distilled off and the residue was triturated with diethyl ether to give 8-(2-aminoacetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine (215 mg).

mp : 180 to 183 °C
 IR (Nujol) : 3300, 3120, 1690, 1605, 1540, 1280 cm^{-1}
 NMR (CDCl₃, δ) : 1.80 (2H, broad s), 2.08 (1H, t, J=3Hz), 2.45 (6H, s), 3.45 (2H, s), 3.77 (2H, d,

J = 3Hz), 5.37 (2H, s), 6.57-6.87 (2H, m), 7.03 (1H, d, J = 8Hz), 7.28 (1H, t, J = 8Hz), 7.80 (1H, dd, J = 2Hz, 6Hz), 7.93 (1H, d, J = 8Hz), 9.90 (1H, broad s)

Example 10

To a solution of 8-(2-amino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine (9.3 g) in dichloromethane (140 ml) was added dropwise benzoyl isothiocyanate and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure and the residue was triturated with ether (50 ml) to give a crystalline product. The crystals were recrystallized from ethanol to give 8-{2-[3-(benzoyl)-thioureido]-6-methylbenzyloxy}-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine (11.7 g).

mp : 159-160 °C
 IR (Nujol) : 3290, 3270, 1645, 1525, 1255 cm⁻¹
 NMR (CDCl₃, δ) : 2.06 (1H, t, J = 3Hz), 2.40 (3H, s), 2.49 (3H, s), 3.40 (2H, d, J = 3Hz), 5.30 (2H, s), 6.60-6.86 (2H, m), 7.13-7.90 (9H, m), 9.20 (1H, br s), 12.23 (1H, br s)

Example 11

To a solution of 8-{2-[3-(benzoyl)thioureido]-6-methylbenzyloxy}-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine (1.08 g) in methanol (6.5 ml) and tetrahydrofuran (19 ml) was added a solution of potassium carbonate (0.32 g) in water (6.5 ml) and the mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with water (150 ml) and then the precipitates were collected by filtration. The precipitates were recrystallized from an aqueous ethanol to give 2-methyl-8-(6-methyl-2-thioureido-benzyloxy)-3-(2-propynyl)imidazo[1,2-a]pyridine (0.55 g).

mp : 155 to 153 °C
 IR (Nujol) : 3460, 3340, 3300, 3150, 1600, 1545 cm⁻¹
 NMR (DMSO-d₆, δ) : 2.29 (3H, s), 2.36 (3H, s), 2.96 (1H, t, J = 3Hz), 3.89 (2H, d, J = 3Hz), 5.15 (2H, s), 6.70-7.0 (2H, m), 7.06-7.53 (5H, m), 7.88 (1H, dd, J = 2, 6Hz), 9.46 (1H, s)

Analysis Calcd. for C₂₀H₂₀N₄OS :

	C 65.91,	H 5.53,	N 15.37
Found :	C 65.91,	H 5.48,	N 15.30

Example 12

The following compounds were prepared according to a similar manner to that of Example 3.

(1) 2-Methyl-8-(6-methyl-2-ureidobenzyloxy)-3-(2-propynyl)imidazo[1,2-a]pyridine

IR (Nujol) : 3380, 3270, 3240, 3170, 1660, 1590, 1540, 1090 cm⁻¹

(2) 8-(2-Formamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

IR (Nujol) : 3200, 1685, 1605, 1585, 1540, 1280 cm⁻¹

(3) 8-(2-Ethoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

IR (Nujol) : 3280, 1710, 1540 cm⁻¹

(4) 8-(2-Methanesulfonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

IR (Nujol) : 3275, 1540, 1323, 1145 cm⁻¹

(5) 8-(3-Acetamido-2-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

IR (Nujol) : 3200, 1635, 1540 cm⁻¹

(6) 2-Methyl-8-[6-methyl-2-(3-methylureido)benzyloxy]-3-(2-propynyl)imidazo[1,2-a]pyridine

IR (Nujol) : 3400, 3290, 1695, 1605 cm⁻¹

(7) 8-(5-Acetamido-2-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

IR (Nujol) : 3270, 1670, 1595, 1535, 1490 cm⁻¹

(8) 8-(2-t-Butoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

IR (CHCl₃) : 3400, 3300, 1710, 1580, 1535, 1370, 1270, 1150 cm⁻¹

(9) 8-(2-Acetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

IR (Nujol) : 3340, 3270, 1683, 1603, 1585, 1280 cm⁻¹

(10) 2-Methyl-3-(2-propynyl)-8-(2-pyruvamido-6-methylbenzyloxy)imidazo[1,2-a]pyridine

IR (Nujol) : 3330, 3260, 1725, 1690, 1600, 1545 cm⁻¹

(11) 8-(2-n-Butyramido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

- IR (Nujol) : 3275, 1680, 1600, 1583, 1535 cm^{-1}
- (12) 2-Methyl-8-(2-methoxalylamino-6-methylbenzyloxy)-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3300, 1738, 1680, 1605, 1585, 1540 cm^{-1}
- (13) 2-Methyl-3-(2-propynyl)-8-(2-sulfamido-6-methylbenzyloxy)imidazo[1,2-a]pyridine
5 IR (Nujol) : 3400, 3310, 3270, 1570, 1545 cm^{-1}
- (14) 8-(2-Lactamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3320, 3270, 1675, 1540, 1275, 1080 cm^{-1}
- (15) 8-(2-Aminoacetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3300, 3120, 1690, 1605, 1540, 1280 cm^{-1}
- 10 (16) 8-{2-[3-(Benzoyl)thioureido]-6-methylbenzyloxy}-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3290, 3270, 1645, 1525, 1255 cm^{-1}
- (17) 2-Methyl-8-(6-methyl-2-thioureidobenzoyloxy)-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3460, 3340, 3300, 3150, 1600, 1545 cm^{-1}

15 Example 13

The following compounds were prepared according to a similar manner to that of Example 1.

- (1) 8-(2-Isonicotinamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3375, 3245, 1680, 1600, 1540, 1520 cm^{-1}
- 20 (2) 2-Methyl-8-(2-methyl-6-propionamidobenzoyloxy)-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3310, 1690, 1600, 1585, 1540 cm^{-1}
- (3) 8-(2-t-Butoxycarbonylaminoacetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]-
pyridine
NMR (CDCl_3 , δ) : 1.30 (9H, s), 2.08 (1H, t, J = 3Hz), 2.47 (6H, s), 3.78 (2H, d, J = 3Hz), 4.03 (2H, d,
25 J = 6Hz), 5.42 (2H, s), 6.70-7.40 (5H, m), 7.77-8.10 (2H, m), 9.67 (1H, broad s)
- (4) 8-(2-Benzoyloxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3290, 1705, 1540 cm^{-1}
- (5) 8-(2-Isopropoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3280, 1705, 1540 cm^{-1}
- 30 (6) 8-(4-Acetamido-2-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3250, 1680, 1590, 1540 cm^{-1}
- (7) 8-(2-Hydroxyacetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3320, 3190, 1680, 1520, 1280 cm^{-1}
- (8) 8-(2-Acetoxyacetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
NMR (Nujol) : 3390, 3275, 1740, 1685, 1600, 1525, 1270, 1220 cm^{-1}
- 35 (9) 2-Methyl-3-(2-propynyl)-8-(2-pyruvamido-6-methylbenzyloxy)imidazo[1,2-a]pyridine
IR (Nujol) : 3330, 3260, 1725, 1690, 1600, 1545 cm^{-1}
- (10) 8-(2-n-Butyramido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3275, 1680, 1600, 1583, 1535 cm^{-1}
- 40 (11) 2-Methyl-8-(2-methoxalylamino-6-methylbenzyloxy)-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3300, 1738, 1680, 1605, 1585, 1540 cm^{-1}
- (12) 2-Methyl-3-(2-propynyl)-8-(2-sulfamido-6-methylbenzyloxy)imidazo[1,2-a]pyridine
IR (Nujol) : 3400, 3310, 3270, 1570, 1545 cm^{-1}
- (13) 8-(2-Lactamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
45 IR (Nujol) : 3320, 3270, 1675, 1540, 1275, 1080 cm^{-1}
- (14) 8-(2-Aminoacetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3300, 3120, 1690, 1605, 1540, 1280 cm^{-1}
- (15) 8-{2-[3-(Benzoyl)thioureido]-6-methylbenzyloxy}-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3290, 3270, 1645, 1525, 1255 cm^{-1}
- 50 (16) 2-Methyl-8-(6-methyl-2-thioureidobenzoyloxy)-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3460, 3340, 3300, 3150, 1600, 1545 cm^{-1}

Example 14

55 The following compounds were prepared according to a similar manner to that of Example 5.

- (1) 2-Methyl-8-(6-methyl-2-ureidobenzoyloxy)-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3380, 3270, 3240, 3170, 1660, 1590, 1540, 1090 cm^{-1}
- (2) 8-(2-Formamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine

- IR (Nujol) : 3200, 1685, 1605, 1585, 1540, 1280 cm^{-1}
- (3) 8-(2-Ethoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3280, 1710, 1540 cm^{-1}
- (4) 8-(2-Methanesulfonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3275, 1540, 1323, 1145 cm^{-1}
- (5) 8-(3-Acetamido-2-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3200, 1635, 1540 cm^{-1}
- (6) 2-Methyl-8-[6-methyl-2-(3-methylureido)benzyloxy]-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3400, 3290, 1695, 1605 cm^{-1}
- (7) 8-(2-Methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3300, 1710, 1535, 1360, 1275, 1255 cm^{-1}
- (8) 8-(5-Acetamido-2-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3270, 1670, 1595, 1535, 1400 cm^{-1}
- (9) 8-(2-t-Butoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (CHCl_3) : 3400, 3300, 1710, 1580, 1535, 1370, 1270, 1150 cm^{-1}
- (10) 8-(2-Acetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3340, 3270, 1683, 1603, 1585, 1280 cm^{-1}
- (11) 8-(2-Isonicotinamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3375, 3245, 1680, 1600, 1540, 1520 cm^{-1}
- (12) 2-Methyl-8-(2-methyl-6-propionamidobenzyloxy)-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3310, 1690, 1600, 1585, 1540 cm^{-1}
- (13) 8-(2-t-Butoxycarbonylaminoacetamido-6-methyl benzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]-pyridine
NMR (CDCl_3 , δ) : 1.30 (9H, s), 2.08 (1H, t, J=3Hz), 2.47 (6H, s), 3.78 (2H, d, J=3Hz), 4.03 (2H, d, J=6Hz), 5.42 (2H, s), 6.70-7.40 (5H, m), 7.77-8.10 (2H, m), 9.67 (1H, broad s)
- (14) 8-(2-Benzyloxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3290, 1705, 1540 cm^{-1}
- (15) 8-(2-Isopropoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3280, 1705, 1540 cm^{-1}
- (16) 8-(4-Acetamido-2-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3250, 1680, 1590, 1540 cm^{-1}
- (17) 8-(2-Hydroxyacetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3320, 3190, 1680, 1520, 1280 cm^{-1}
- (18) 8-(2-Acetoxyacetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3390, 3275, 1740, 1685, 1600, 1525, 1270, 1220 cm^{-1}
- (19) 8-(2-Lactamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3320, 3270, 1675, 1540, 1275, 1080 cm^{-1}
- (20) 8-(2-Aminoacetamido-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3300, 3120, 1690, 1605, 1540, 1280 cm^{-1}
- (21) 8-{2-(3-Benzoylthioureido)-6-methylbenzyloxy}-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3290, 3270, 1645, 1525, 1255 cm^{-1}
- (22) 2-Methyl-8-(6-methyl-2-thioureidobenzyloxy)-3-(2-propynyl)imidazo[1,2-a]pyridine
IR (Nujol) : 3460, 3340, 3300, 3150, 1600, 1545 cm^{-1}

45 Example 15

A mixture of 8-hydroxy-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine (0.372 g) and potassium carbonate (0.276 g) in N,N-dimethylformamide (7.4 ml) was stirred at room temperature for 20 minutes under a nitrogen atmosphere and then 2-methoxycarbonylamino-6-methylbenzylchloride (0.427 g) was added. After being stirred for 2 hours, the mixture was poured into water and the resulting precipitates were collected by filtration. The crude product was purified by column chromatography on silica gel (10 g) with chloroform as eluents to give 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine (0.048 g).

mp : 180 to 181 ° C (recrystallized from a mixture of ethyl acetate and cyclohexane)

IR (Nujol) : 3300, 1710, 1535, 1360, 1275, 1255 cm^{-1}

NMR (CDCl_3 , δ) : 2.06 (1H, t, J=3Hz), 2.48 (6H, s), 3.73 (3H, s), 3.75 (2H, d, J=3Hz), 5.35 (2H, s), 6.53-6.80 (2H, m), 6.90 (1H, d, J=7.5Hz), 7.18 (1H, t, J=7.5Hz), 7.50-7.80 (2H, m), 9.17 (1H, broad s)

Example 16

8-(2-Methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-a]pyridine
(Compound 1) prepared by Example 3, 14-(7) or 15 can be obtained as A-form as B-form according to the following methods.

(1) Compound 1 (50.0 g) was dissolved in ethanol (1,500 ml) under reflux and the hot solution was poured into water (1,500 ml). The precipitate formed was collected by filtration, washed with ethanol and dried under vacuum to give the crystals of A-form (47.4 g).

IR (Nujol) : 3300, 1710, 1535, 1360, 1275, 1255 cm^{-1}

X-ray powder diffraction : $2\theta = 8.8^\circ$

Similarly, the crystals of A-form could be obtained by recrystallization of Compound 1 from the following solvents :

Solvents

ethyl acetate-cyclohexane, tetrahydrofuran-water, isopropylalcohol-water, ethyl acetate-heptane

(2) Compound 1 (50.0 g) was dissolved in ethyl acetate (850 ml) under reflux and cooled at 10°C . The precipitate formed was collected by filtration, washed with ethyl acetate, and dried under vacuum to give the crystals of B-form (43.2 g).

IR (Nujol) : 3300, 1710, 1535, 1360, 1275, 1255, 1245 cm^{-1}

X-ray powder diffraction : $2\theta = 9.2^\circ$

Similarly, the crystals of B-form could be obtained by recrystallization of Compound 1 from the following solvents :

Solvents

tetrahydrofuran, acetonitrile, methylene chloride, methyl ethyl ketone, methyl isobutyl ketone, tetrahydrofuran-heptane, acetonitrile-heptane

(3) Compound 1 (5.0 g) was dissolved in ethanol (75 ml) under reflux and allowed to stand. After an hour, the solution was cooled at 10°C . The precipitate formed was collected by filtration, washed with ethanol, and dried under vacuum to give the crystals of the mixture of A-form and B-form (4.62 g).

Similarly, the crystals of the mixture of A-form and B-form could be obtained by recrystallization of Compound 1 from the following solvent :

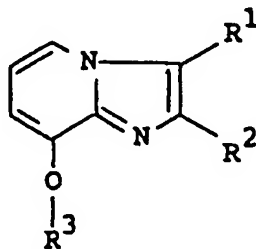
Solvent

ethanol-cyclohexane

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. An imidazopyridine compound of the formula :



wherein

R¹ is C₂-C₆ alkynyl,

R² is C₁-C₆ alkyl, and

R^3 is benzyl substituted by C_1 - C_6 alkyl and one additional substituent selected from C_1 - C_6 alkanoylamino, C_1 - C_6 alkanesulfonylamino, C_1 - C_6 alkoxy-carbonylamino, isonicotinamido, ureido, ureido having C_1 - C_6 alkyl, C_1 - C_6 alkoxy-carbonylamino(C_1 - C_6)alkanoylamino, phenyl(C_1 - C_6)alkoxy-carbonylamino, 3-benzoylthioureido, thioureido, C_1 - C_6 alkanoyloxy(C_1 - C_6)alkanoylamino, C_1 - C_6 alkanoylcarbonylamino, C_1 - C_6 alkoxy-carbonylcarbonylamino, sulfamido, C_1 - C_6 alkanoylamino having hydroxy and amino(C_1 - C_6)alkanoylamino, and a pharmaceutically acceptable salt thereof.

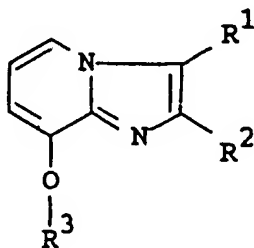
2. A compound of claim 1, wherein

R^1 is propynyl,
 R^2 is methyl, and
 R^3 is benzyl substituted by methyl and one additional substituent selected from formamido, acetamido, propionamido, n-butyramido, methanesulfonylamino, methoxycarbonylamino, ethoxycarbonylamino, iso-propoxycarbonylamino, tert-butoxycarbonylamino, isonicotinamido, ureido, methylureido, tert-butoxycarbonylaminoacetamido, benzyloxycarbonylamino, 3-benzoylthioureido, thioureido hydroxyacetamido, acetoxycetamido, pyruvamido, methoxalylamino, sulfamido, lactamido and aminoacetamido.

3. A compound of claim 2, wherein

R^1 is 2-propynyl, and
 R^3 is 2-formamido-6-methylbenzyl, 2-acetamido-6-methylbenzyl, 3-acetamido-2-methylbenzyl, 4-acetamido-2-methylbenzyl, 5-acetamido-2-methylbenzyl, 2-methyl-6-propionamidobenzyl, 2-n-butyramido-6-methylbenzyl, 2-methanesulfonylamino-6-methylbenzyl, 2-methoxycarbonylamino-6-methylbenzyl, 2-ethoxycarbonylamino-6-methylbenzyl, 2-iso-propoxycarbonylamino-6-methylbenzyl, 2-methyl-6-tert-butoxycarbonylamino-benzyl, 2-isonicotinamido-6-methylbenzyl, 2-methyl-6-ureidobenzyl, 2-methyl-6-(3-methylureido)benzyl, 2-methyl-6-tert-butoxycarbonylaminoacetamidobenzyl, 2-benzyloxycarbonylamino-6-methylbenzyl, 2-(3-benzoylthioureido)-6-methylbenzyl, 2-methyl-6-thioureidobenzyl, 2-hydroxyacetamido-6-methylbenzyl, 2-acetoxycetamido-6-methylbenzyl, 2-methyl-6-pyruvamidobenzyl, 2-methoxalylamino-6-methylbenzyl, 2-methyl-6-sulfamidobenzyl, 2-lactamido-6-methylbenzyl, 2-aminoacetamido-6-methylbenzyl.

4. A process for preparing imidazopyridine compounds of the formula :



wherein

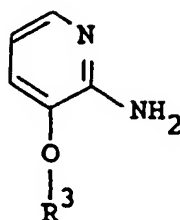
R^1 is C_2 - C_6 alkynyl,
 R^2 is C_1 - C_6 alkyl, and
 R^3 is benzyl substituted by C_1 - C_6 alkyl and one additional substituent selected from C_1 - C_6 alkanoylamino, C_1 - C_6 alkanesulfonylamino, C_1 - C_6 alkoxy-carbonylamino, isonicotinamido, ureido, ureido having C_1 - C_6 alkyl, C_1 - C_6 alkoxy-carbonylamino(C_1 - C_6)alkanoylamino, phenyl(C_1 - C_6)alkoxy-carbonylamino, 3-benzoylthioureido, thioureido, C_1 - C_6 alkanoyloxy(C_1 - C_6)alkanoylamino, C_1 - C_6 alkanoylcarbonylamino, C_1 - C_6 alkoxy-carbonylcarbonylamino, sulfamido, C_1 - C_6 alkanoylamino having hydroxy and amino(C_1 - C_6)alkanoylamino,

or a salt thereof,

which comprises

(1) reacting a compound of the formula :

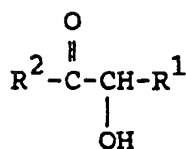
5



10

wherein R³ is as defined above,
or a salt thereof,
with a compound of the formula :

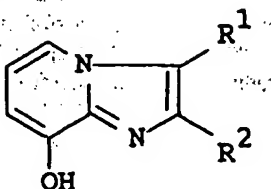
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wherein R¹ and R² are each as defined above,
or its reactive derivative at the hydroxy group, or
(2) reacting a compound of the formula :

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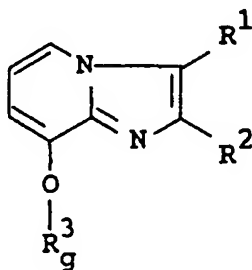
wherein R¹ and R² are each as defined above,
or a salt thereof,
with a compound of the formula :

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R³ - OH

wherein R³ is as defined above,
or its reactive derivative at the hydroxy group, or
(3) subjecting a compound of the formula :

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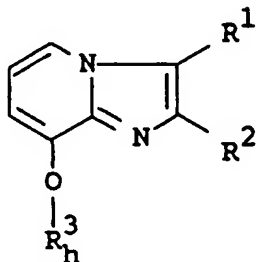


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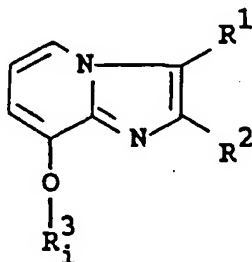
wherein
R¹ and R² are each as defined above, and

R_g^3 is benzyl substituted by C_1 - C_6 alkyl and C_1 - C_6 alkanoylcarbonylamino, or a salt thereof, to reduction reaction, to give a compound of the formula :



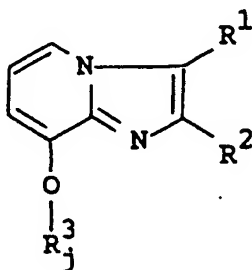
wherein

R^1 and R^2 are each as defined above, and R_h^3 is benzyl substituted by C_1 - C_6 alkyl and α -hydroxy(C_1 - C_6)alkanoylamino, or a salt thereof, or
(4) subjecting a compound of the formula :



wherein

R^1 and R^2 are each as defined above, and R_i^3 is benzyl substituted by C_1 - C_6 alkyl and one additional substituent selected from C_1 - C_6 alkoxycarbonylamino(lower)alkanoylamino and 3-benzoyl thioureido, or a salt thereof, to elimination reaction of the amino protective group to give a compound of the formula :



wherein

R^1 and R^2 are each as defined above, and R_j^3 is benzyl substituted by C_1 - C_6 alkyl and one additional substituent selected from amino(C_1 - C_6)alkanoylamino and thioureido,

or a salt thereof.

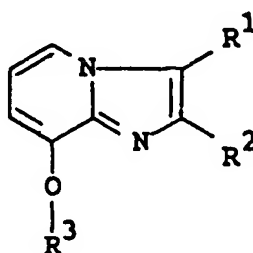
5. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

6. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

7. A compound of claim 1 or pharmaceutically acceptable salt thereof for the use as a medicament for treating ulcer.

Claim for the following Contracting State : ES

1. A process for preparing imidazopyridine compounds of the formula :



wherein

R¹ is C₂-C₆ alkynyl,

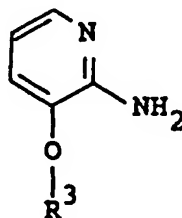
R² is C₁-C₆ alkyl, and

R³ is benzyl substituted by C₁-C₆ alkyl and one additional substituent selected from C₁-C₆ alkanoylamino, C₁-C₆ alkanesulfonylamino, C₁-C₆ alkoxy-carbonylamino, isonicotinamido, ureido, ureido having C₁-C₆ alkyl, C₁-C₆ alkoxy-carbonylamino(C₁-C₆)alkanoylamino, phenyl(C₁-C₆)alkoxy-carbonylamino, 3-benzoylthioureido, thioureido, C₁-C₆ alkanoyloxy(C₁-C₆)alkanoylamino, C₁-C₆ alkanoylcarbonylamino, C₁-C₆ alkoxy-carbonylcarbonylamino, sulfamido, C₁-C₆ alkanoylamino having hydroxy and amino(C₁-C₆)alkanoylamino,

or a salt thereof,

which comprises

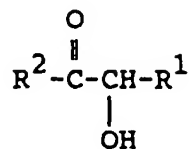
(1) reacting a compound of the formula :



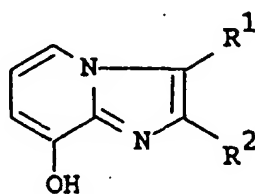
wherein R³ is as defined above,

or a salt thereof,

with a compound of the formula :



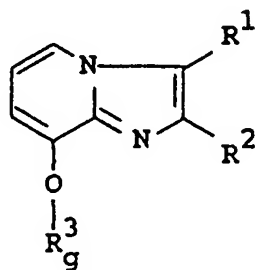
wherein R¹ and R² are each as defined above,
or its reactive derivative at the hydroxy group, or
(2) reacting a compound of the formula :



wherein R¹ and R² are each as defined above,
or a salt thereof,
with a compound of the formula :

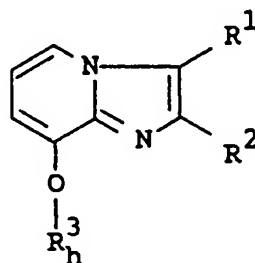


wherein R³ is as defined above,
or its reactive derivative at the hydroxy group, or
(3) subjecting a compound of the formula :



wherein

R¹ and R² are each as defined above, and
R_g³ is benzyl substituted by C₁-C₆ alkyl and C₁-C₆ alkanoylcarbonylamino,
or a salt thereof, to reduction reaction,
to give a compound of the formula :



wherein

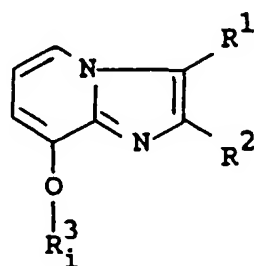
R^1 and R^2 are each as defined above, and

R_h^3 is benzyl substituted by C_1-C_6 alkyl and α -hydroxy(C_1-C_6)alkanoylamino,

or a salt thereof,

or

(4) subjecting a compound of the formula :

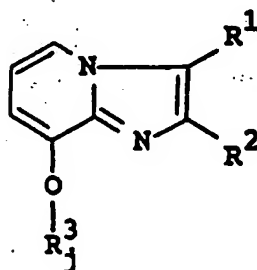


wherein

R^1 and R^2 are each as defined above, and

R_i^3 is benzyl substituted by C_1-C_6 alkyl and one additional substituent selected from C_1-C_6 alkoxy, carbonylamino, (lower)alkanoylamino and 3-benzoyl thioureido,

or a salt thereof, to elimination reaction of the amino protective group to give a compound of the formula :



wherein

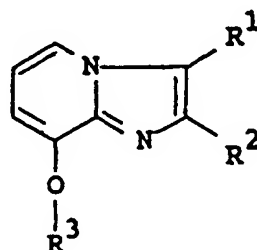
R^1 and R^2 are each as defined above, and

R_j^3 is benzyl substituted by C_1-C_6 alkyl and one additional substituent selected from amino(C_1-C_6)alkanoylamino and thioureido,

or a salt thereof.

Claims for the following Contracting State : GR

1. A process for preparing imidazopyridine compounds of the formula :



wherein

R¹ is C₂-C₆ alkynyl,

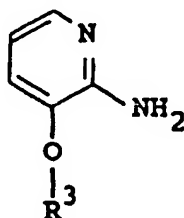
R² is C₁-C₆ alkyl, and

R³ is benzyl substituted by C₁-C₆ alkyl and one additional substituent selected from C₁-C₆ alkanoylamino, C₁-C₆ alkanesulfonylamino, C₁-C₆ alkoxy-carbonylamino, isonicotinamido, ureido, ureido having C₁-C₆ alkyl, C₁-C₆ alkoxy-carbonylamino(C₁-C₆)alkanoylamino, phenyl(C₁-C₆)alkoxy-carbonylamino, 3-benzoylthioureido, thioureido, C₁-C₆ alkanoyloxy(C₁-C₆)alkanoylamino, C₁-C₆ alkanoylcarbonylamino, C₁-C₆ alkoxy-carbonylcarbonylamino, sulfamido, C₁-C₆ alkanoylamino having hydroxy and amino(C₁-C₆)alkanoylamino,

or a salt thereof,

which comprises

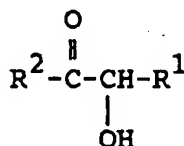
(1) reacting a compound of the formula :



wherein R³ is as defined above,

or a salt thereof,

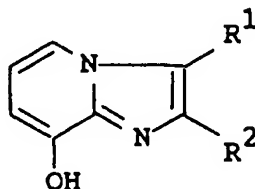
with a compound of the formula :



wherein R¹ and R² are each as defined above,

or its reactive derivative at the hydroxy group, or

(2) reacting a compound of the formula :



wherein R¹ and R² are each as defined above,

or a salt thereof,

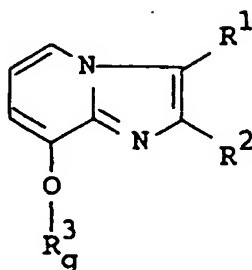
with a compound of the formula :

R³ - OH

wherein R³ is as defined above,

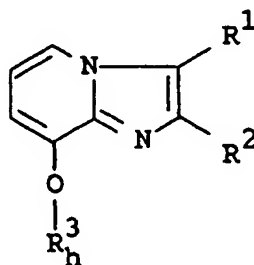
or its reactive derivative at the hydroxy group, or

(3) subjecting a compound of the formula :



wherein

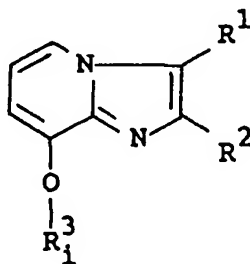
R^1 and R^2 are each as defined above, and
 R^3_g is benzyl substituted by C_1 - C_6 alkyl and C_1 - C_6 alkanoylcarbonylamino,
 or a salt thereof, to reduction reaction,
 to give a compound of the formula :



wherein

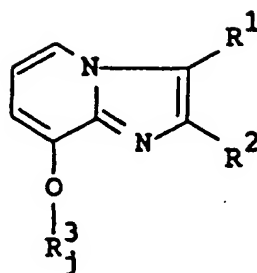
R^1 and R^2 are each as defined above, and
 R^3_h is benzyl substituted by C_1 - C_6 alkyl and α -hydroxy(C_1 - C_6)alkanoylamino,
 or a salt thereof,
 or

(4) subjecting a compound of the formula :



wherein

R^1 and R^2 are each as defined above, and
 R^3_i is benzyl substituted by C_1 - C_6 alkyl and one additional substituent selected from
 C_1 - C_6 alkoxy carbonylamino(lower)alkanoylamino and 3-benzoyl thioureido,
 or a salt thereof, to elimination reaction of the amino protective group to give a compound of the
 formula :



wherein

R¹ and R² are each as defined above, and
R³ is benzyl substituted by C₁-C₆ alkyl and one additional substituent selected from
amino(C₁-C₆)alkanoylamino and thioureido,

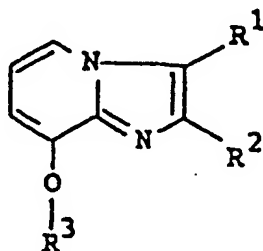
or a salt thereof.

2. Modification of the process claimed in claim 1 which is characterized by bringing a compound, prepared by a process of claim 1, into pharmaceutically acceptable form by admixture or presentation of said compound with a pharmaceutically acceptable diluent or carrier.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Imidazopyridine répondant à la formule :



dans laquelle

R¹ est un groupe alcynyle en C₂ à C₆,

R² est un groupe alkyle en C₁ à C₆, et

R³ est un groupe benzyle substitué par un groupe alkyle en C₁ à C₆ et par un substituant supplémentaire choisi parmi un groupe alcanoylamino en C₁ à C₆, alcanesulfonylamino en C₁ à C₆, (alcoxy en C₁ à C₆)carbonylamino, isonicotinamido, uréido, uréido ayant un groupe alkyle en C₁ à C₆ (alcoxy en C₁ à C₆)carbonylamino(alcanoylamino en C₁ à C₆), phényl(alcoxy en C₁ à C₆)carbonylamino, 3-benzoylthiouréido, thiouréido, (alcanoyloxy en C₁ à C₆) (alcanoylamino en C₁ à C₆), (alcanoyloxy en C₁ à C₆)carbonylamino, (alcoxy en C₁ à C₆)carbonylcarbonylamino, sulfamido, alcanoylamino en C₁ à C₆ ayant un groupe hydroxy et amino(alcanoylamino en C₁ à C₆)

et ses sels pharmaceutiquement acceptables.

2. Composé selon la revendication 1, dans lequel

R¹ est un groupe propynyle,

R² est un groupe méthyle, et

R³ est un groupe benzyle substitué par un groupe méthyle et par un substituant supplémentaire choisi parmi les groupes formamido, acétamido, propionamido, n-butyramido, méthanesulfonylamino, méthoxycarbonylamino, éthoxycarbonylamino, isopropoxycarbonylamino, tert-butoxycarbonylamino, isonicotinamido, uréido, méthyluréido, tert-butoxycarbonylaminoacétamido, benzyloxycarbonylamino, 3-benzoylthiouréido, thiouréido, hydroxyacétamido, acétoxyacé-

tamido, pyruvamido, méthoxalylamino, sulfamido, lactamido et aminoacétamido.

3. Composé selon la revendication 2, dans lequel :

- 5 R^1 est un groupe 2-propynyle, et
 R^3 est un groupe 2-formamido-6-méthylbenzyle, 2-acétamido-6-méthylbenzyle, 3-acétamido-2-méthylbenzyle, 4-acétamido-2-méthylbenzyle, 5-acétamido-2-méthylbenzyle, 2-méthyl-6-propionamidobenzyle, 2-n-butylamido-6-méthylbenzyle, 2-méthanefsulfonylamino-6-méthylbenzyle, 2-méthoxycarbonylamino-6-méthylbenzyle, 2-éthoxycarbonylamino-6-méthylbenzyle, 2-isopropoxycarbonylamino-6-méthylbenzyle, 2-méthyl-6-tert-butoxycarbonylamino-6-méthylbenzyle, 2-isonicotinamido-6-méthylbenzyle, 2-méthyl-6-uréidobenzyle, 2-méthyl-6-(3-méthyluréido)-benzyle, 2-méthyl-6-tert-butoxycarbonylaminoacétamidobenzyle, 2-benzoyloxycarbonylamino-6-méthylbenzyle, 2-(3-benzoylthiouréido)-6-méthylbenzyle, 2-méthyl-6-thiouréidobenzyle, 2-hydroxyacétamido-6-méthylbenzyle, 2-acétoxyacétamido-6-méthylbenzyle, 2-méthyl-6-pyruvamidobenzyle, 2-méthoxalylamino-6-méthylbenzyle, 2-méthyl-6-sulfamidobenzyle, 2-lactamido-6-méthylbenzyle, 2-aminoacétamido-6-méthylbenzyle.

4. Procédé de préparation d'imidazopyridines répondant à la formule :



30 dans laquelle

- R^1 est un groupe alcynyle en C_2 à C_6 ,
 R^2 est un groupe alkyle en C_1 à C_6 , et
 R^3 est un groupe benzyle substitué par un groupe alkyle en C_1 à C_6 et par un substituant supplémentaire choisi parmi un groupe alcanoylamino en C_1 à C_6 , alcanesulfonylamino en C_1 à C_6 , (alcoxy en C_1 à C_6)carbonylamino, isonicotinamido, uréido, uréido ayant un groupe alkyle en C_1 à C_6 , (alcoxy en C_1 à C_6)carbonylamino(alcanoylamino en C_1 à C_6), phényl(alcoxy en C_1 à C_6)carbonylamino, 3-benzoylthiouréido, thiouréido, (alcanoyloxy en C_1 à C_6) (alcanoylamino en C_1 à C_6), (alcanoyloxy en C_1 à C_6)carbonylamino, (alcoxy en C_1 à C_6)carbonylcarbonylamino, sulfamido, alcanoylamino en C_1 à C_6 ayant un groupe hydroxy et amino(alcanoylamino en C_1 à C_6),

ou leurs sels, qui comprend

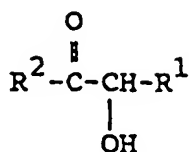
(1) le fait de faire réagir un composé répondant à la formule :



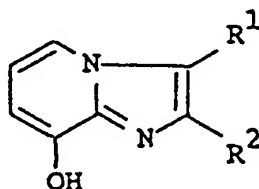
dans laquelle R^3 est tel que défini ci-dessus,

ou un de ses sels,

avec un composé répondant à la formule :



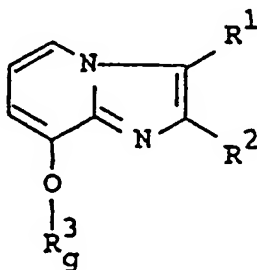
dans laquelle R¹ et R² sont chacun tels que définis ci-dessus,
ou un de ses dérivés réactifs sur le groupe hydroxy, ou
(2) le fait de faire réagir un composé répondant à la formule :



dans laquelle R¹ et R² sont chacun tels que définis ci-dessus,
ou un de ses sels,
avec un composé répondant à la formule :

R³ - OH

dans laquelle R³ est tel que défini ci-dessus,
ou un de ses dérivés réactifs sur le groupe hydroxy,
ou
(3) le fait de soumettre un composé répondant à la formule :

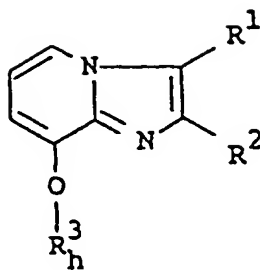


dans laquelle

R¹ et R² sont chacun tels que définis ci-dessus, et
R³ est un groupe benzyle substitué par un groupe alkyle en C₁ à C₆ et un groupe
(alcanoyle en C₁ à C₆)carbonylamino,
ou un de ses sels, à une réaction de réduction,
pour donner un composé répondant à la formule :

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dans laquelle

R¹ et R² sont chacun tels que définis ci-dessus, et
R³h est un groupe benzyle substitué par un groupe alkyle en C₁ à C₆ et un groupe α-hydroxy(alcanoylamino en C₁ à C₆)

ou un de ses sels,

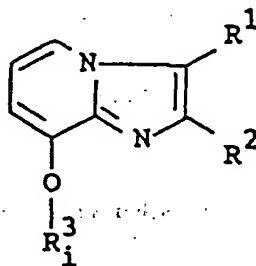
ou

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(4) le fait de soumettre un composé répondant à la formule :

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dans laquelle

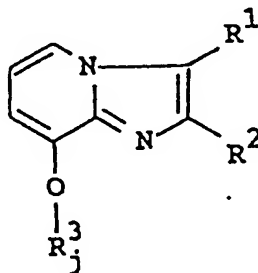
R¹ et R² sont chacun tels que définis ci-dessus, et
R³i est un groupe benzyle substitué par un groupe alkyle en C₁ à C₆ et par un substituant supplémentaire choisi parmi un groupe (alcoxy en C₁ à C₆) carbonylamino(alcanoylamino inférieur) et 3-benzoylthiouréido,

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ou un de ses sels, à une réaction d'élimination du groupe protecteur du groupe amino pour donner un composé répondant à la formule :

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dans laquelle

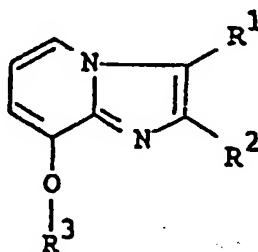
R¹ et R² sont chacun tels que définis ci-dessus, et
R³j est un groupe benzyle substitué par un groupe alkyle en C₁ à C₆ et par un substituant supplémentaire choisi parmi un groupe amino(alcanoylamino en C₁ à

C₆) et thiouréido,
ou un de ses sels.

- 5 5. Composition pharmaceutique qui comprend comme ingrédient actif un composé selon la revendication 1 ou un de ses sels pharmaceutiquement acceptables en mélange avec des supports pharmaceutiquement acceptables.
6. Composé selon la revendication 1 ou un de ses sels pharmaceutiquement acceptables pour l'utilisation comme médicament.
- 10 7. Composé selon la revendication 1 ou un de ses sels pharmaceutiquement acceptables pour l'utilisation comme médicament pour le traitement des ulcères.

Revendication pour l'Etat contractant suivant : ES

- 15 1. Procédé de préparation d'imidazopyridines répondant à la formule :



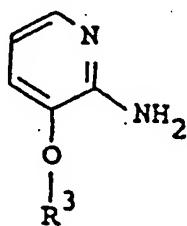
dans laquelle

- R¹ est un groupe alcynyle en C₂ à C₆,
 R² est un groupe alkyle en C₁ à C₆, et
 R³ est un groupe benzyle substitué par un groupe alkyle en C₁ à C₆ et par un substituant supplémentaire choisi parmi un groupe alcanoylamino en C₁ à C₆, alcanesulfonylamino en C₁ à C₆, (alcoxy en C₁ à C₆)carbonylamino, isonicotinamido, uréido, uréido ayant un groupe alkyle en C₁ à C₆ (alcoxy en C₁ à C₆)carbonylamino(alcanoylamino en C₁ à C₆), phényl(alcoxy en C₁ à C₆)carbonyl-amino, 3-benzoylthiouréido, thiouréido, (alcanoyloxy en C₁ à C₆) (alcanoylamino en C₁ à C₆), (alcanoyloxy en C₁ à C₆)carbonylamino, (alcoxy en C₁ à C₆)carbonylcarbonylamino, sulfamido, alcanoylamino en C₁ à C₆ ayant un groupe hydroxy et amino(alcanoylamino en C₁ à C₆),

ou de leurs sels,

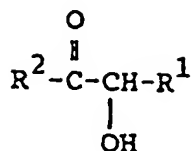
qui comprend

- (1) le fait de faire réagir un composé répondant à la formule :



dans laquelle R³ est tel que défini ci-dessus,
 ou un de ses sels,
 avec un composé répondant à la formule :

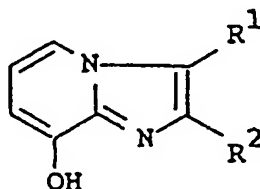
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dans laquelle R¹ et R² sont chacun tels que définis ci-dessus,
ou un de ses dérivés réactifs sur le groupe hydroxy, ou
(2) le fait de faire réagir un composé répondant à la formule :

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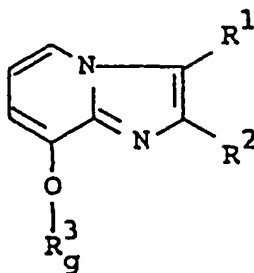
dans laquelle R¹ et R² sont chacun tels que définis ci-dessus,
ou un de ses sels,
avec un composé répondant à la formule :

R³ - OH

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dans laquelle R³ est tel que défini ci-dessus,
ou un de ses dérivés réactifs sur le groupe hydroxy,
ou
(3) le fait de soumettre un composé répondant à la formule :

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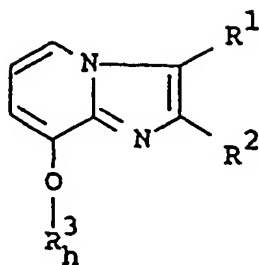
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dans laquelle
R¹ et R² sont chacun tels que définis ci-dessus, et
R³ est un groupe benzyle substitué par un groupe alkyle en C₁ à C₆ et un groupe
(alcanoyle en C₁ à C₆)carbonylamino,
ou un de ses sels, à une réaction de réduction,
pour donner un composé répondant à la formule :

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dans laquelle

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R^1 et R^2 sont chacun tels que définis ci-dessus, et
 R_h^3 est un groupe benzyle substitué par un groupe alkyle en C_1 à C_6 et un groupe α -hydroxy(alcanoylamino en C_1 à C_6)

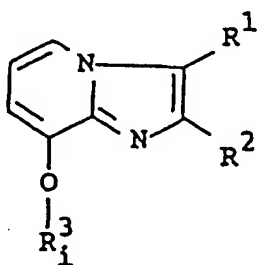
ou un de ses sels,

ou

(4) le fait de soumettre un composé répondant à la formule :

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dans laquelle

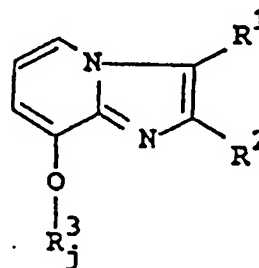
35

R^1 et R^2 sont chacun tels que définis ci-dessus, et
 R_i^3 est un groupe benzyle substitué par un groupe alkyle en C_1 à C_6 et par un substituant supplémentaire choisi parmi un groupe (alcoxy en C_1 à C_6) carbonylamino(alcanoylamino inférieur) et 3-benzoylthiouréido,

ou un de ses sels, à une réaction d'élimination du groupe protecteur du groupe amino pour donner un composé répondant à la formule :

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dans laquelle

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R^1 et R^2 sont chacun tels que définis ci-dessus, et
 R_j^3 est un groupe benzyle substitué par un groupe alkyle en C_1 à C_6 et par un substituant supplémentaire choisi parmi un groupe amino(alcanoylamino en C_1 à C_6) et thiouréido,

ou un de ses sels.

Revendications pour l'Etat contractant suivant : GR

- 5 1. Procédé de préparation d'imidazopyridines répondant à la formule :

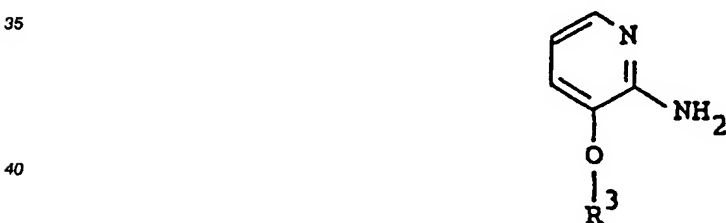


dans laquelle

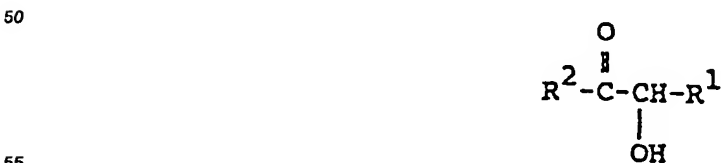
- 20 R¹ est un groupe alcynyle en C₂ à C₆,
 R² est un groupe alkyle en C₁ à C₆, et
 R³ est un groupe benzyle substitué par un groupe alkyle en C₁ à C₆ et par un substituant
 supplémentaire choisi parmi un groupe alcanoylamino en C₁ à C₆, alcanesulfonylamino en C₁
 à C₆, (alcoxy en C₁ à C₆)carbonylamino, isonicotinamido, uréido, uréido ayant un groupe
 25 alkyle en C₁ à C₆ (alcoxy en C₁ à C₆)carbonylamino(alcanoylamino en C₁ à C₆),
 phényl(alcoxy en C₁ à C₆)carbonylamino, 3-benzoylthiouréido, thiouréido, (alcanoyloxy en C₁
 à C₆) (alcanoylamino en C₁ à C₆), (alcanoyloxy en C₁ à C₆)carbonylamino, (alcoxy en C₁ à
 C₆)carbonylcarbonylamino, sulfamido, alcanoylamino en C₁ à C₆ ayant un groupe hydroxy et
 amino(alcanoylamino en C₁ à C₆)

30 ou de leurs sels,
 qui comprend

- (1) le fait de faire réagir un composé répondant à la formule :



45 dans laquelle R³ est tel que défini ci-dessus,
 ou un de ses sels,
 avec un composé répondant à la formule :

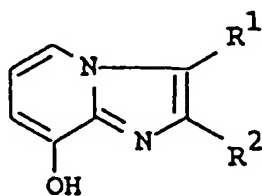


dans laquelle R¹ et R² sont chacun tels que définis ci-dessus,

ou un de ses dérivés réactifs sur le groupe hydroxy, ou
(2) le fait de faire réagir un composé répondant à la formule :

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dans laquelle R¹ et R² sont chacun tels que définis ci-dessus,
ou un de ses sels,
avec un composé répondant à la formule :

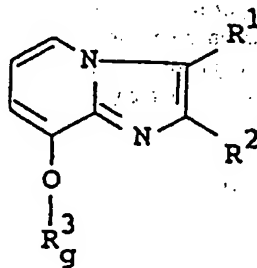
R³ - OH

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dans laquelle R³ est tel que défini ci-dessus,
ou un de ses dérivés réactifs sur le groupe hydroxy,
ou
(3) le fait de soumettre un composé répondant à la formule :

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dans laquelle

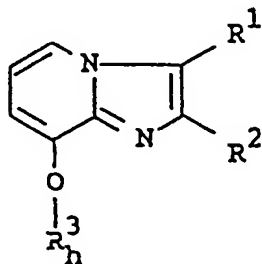
40

R¹ et R² sont chacun tels que définis ci-dessus, et
R³ est un groupe benzyle substitué par un groupe alkyle en C₁ à C₆ et un groupe
(alcanoyl en C₁ à C₆)carbonylamino,
ou un de ses sels, à une réaction de réduction,
pour donner un composé répondant à la formule :

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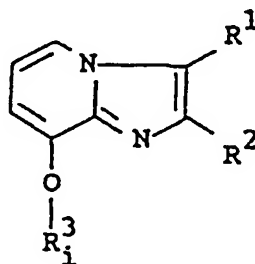
dans laquelle

R¹ et R² sont chacun tels que définis ci-dessus, et
R_h³ est un groupe benzyle substitué par un groupe alkyle en C₁ à C₆ et un groupe α-hydroxy(alcanoylamino en C₁ à C₆)

ou un de ses sels,

ou

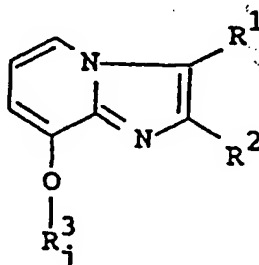
(4) le fait de soumettre un composé répondant à la formule :



dans laquelle

R¹ et R² sont chacun tels que définis ci-dessus, et
R_i³ est un groupe benzyle substitué par un groupe alkyle en C₁ à C₆ et par un substituant supplémentaire choisi parmi un groupe (alcoxy en C₁ à C₆) carbonylamino(alcanoylamino inférieur) et 3-benzoylthiouréido,

ou un de ses sels, à une réaction d'élimination du groupe protecteur du groupe amino pour donner un composé répondant à la formule :



dans laquelle

R¹ et R² sont chacun tels que définis ci-dessus, et
R_j³ est un groupe benzyle substitué par un groupe alkyle en C₁ à C₆ et par un substituant supplémentaire choisi parmi un groupe amino(alcanoylamino en C₁ à C₆) et thiouréido,

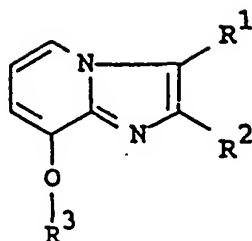
ou un de ses sels.

2. Variante du procédé selon la revendication 1, caractérisée en ce qu'on amène un composé préparé par le procédé selon la revendication 1 sous une forme pharmaceutiquement acceptable par mélange ou présentation de ce composé avec un diluant ou support pharmaceutiquement acceptable.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Imidazopyridinverbindung der Formel



worin

R¹ die Bedeutung C₂-C₆-Alkynyl hat,

R² ist C₁-C₆-Alkyl und

R³ ist Benzyl, substituiert durch C₁-C₆-Alkyl und einen zusätzlichen Substituenten, ausgewählt unter C₁-C₆-Alkanoylamino, C₁-C₆-Alkansulfonylamino, C₁-C₆-Alkoxy-carbonylamino, Isonicotinamido, Ureido, Ureido mit C₁-C₆-Alkyl, C₁-C₆-Alkoxy-carbonylamino(C₁-C₆)-alkanoylamino, Phenyl(C₁-C₆)-alkoxy-carbonylamino, 3-Benzoylthioureido, Thioureido, C₁-C₆-Alkanoyloxy(C₁-C₆)-alkanoylamino, C₁-C₆-Alkanoyl-carbonylamino, C₁-C₆-Alkoxy-carbonyl-carbonylamino, Sulfamido, C₁-C₆-Alkanoylamino mit Hydroxy, und Amino(C₁-C₆)-alkanoylamin, und ein pharmazeutisch annehmbares Salz davon.

2. Verbindung nach Anspruch 1, worin

R¹ Propinyl ist,

R² ist Methyl und

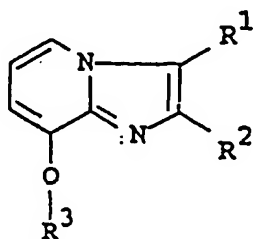
R³ ist Benzyl, substituiert durch Methyl und einen zusätzlichen Substituenten, ausgewählt unter Formamido, Acetamido, Propionamido, n-Butyramido, Methansulfonylamino, Methoxycarbonylamino, Ethoxycarbonylamino, iso-Propoxycarbonylamino, tert.-Butoxycarbonylamino, Isonicotinamido, Ureido, Methylureido, tert.-Butoxycarbonylaminoacetamido, Benzoyloxycarbonylamino, 3-Benzoylthioureido, Thioureido, hydroxyacetamido, Acetoxyacetamido, Pyruvamido, Methoxalylamino, Sulfamido, Lactamido und Aminoacetamido.

3. Verbindung nach Anspruch 2, worin

R¹ 2-Propinyl ist, und

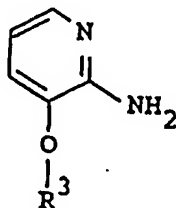
R³ ist 2-Formamido-6-methylbenzyl, 2-Acetamido-6-methylbenzyl, 3-Acetamido-2-methylbenzyl, 3-Acetamido-2-methylbenzyl, 4-Acetamido-2-methylbenzyl, 5-Acetamido-2-methylbenzyl, 2-Methyl-6-propionamidobenzyl, 2-n-Butyramido-6-methylbenzyl, 2-Methansulfonylamino-6-methylbenzyl, 2-Methoxycarbonylamino-6-methylbenzyl, 2-Ethoxycarbonylamino-6-methylbenzyl, 2-iso-Propoxycarbonylamino-6-methylbenzyl, 2-Methyl-6-tert.-butoxycarbonylaminobenzyl, 2-Isonicotinamido-6-methylbenzyl, 2-Methyl-6-ureidobenzyl, 2-Methyl-6-(3-methylureido)benzyl, 2-Methyl-6-tert.-butoxycarbonylaminoacetamidobenzyl, 2-(3-Benzoylthioureido)-6-methylbenzyl, 2-Methyl-6-thioureidobenzyl, 2-Hydroxyacetamido-6-methylbenzyl, 2-Acetoxyacetamido-6-methylbenzyl, 2-Methyl-6-pyruvamidobenzyl, 2-Methoxalylamino-6-methylbenzyl, 2-Methyl-6-sulfamidobenzyl, 2-Lactamido-6-methylbenzyl, 2-Aminoacetamido-6-methylbenzyl.

4. Verfahren zur Herstellung von Imidazopyridinverbindungen der Formel

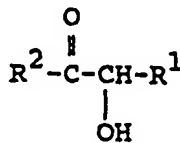


worin R^1 die Bedeutung C_2 - C_6 -Alkynyl hat, R^2 ist C_1 - C_6 -Alkyl und R^3 ist Benzyl substituiert durch C_1 - C_6 -Alkyl und einen zusätzlichen Substituenten, ausgewählt unter C_1 - C_6 -Alkanoylamino, C_1 - C_6 -Alkansulfonylamino, C_1 - C_6 -Alkoxy-carbonylamino, Isonicotinamido, Ureido, Ureido mit C_1 - C_6 -Alkyl, C_1 - C_6 -Alkoxy-carbonylamino(C_1 - C_6)alkanoylamino, Phenyl(C_1 - C_6)-alkoxy-carbonylamino, 3-Benzoylthioureido, Thioureido, C_1 - C_6 -Alkanoyloxy(C_1 - C_6)alkanoylamino, C_1 - C_6 -Alkanoyl-carbonylamino, C_1 - C_6 -Alkoxy-carbonyl-carbonylamino, Sulfamido, C_1 - C_6 -Alkanoylamino mit Hydroxy, und Amino(C_1 - C_6)alkanoylamino, oder eines Salzes davon, umfassend

(1) die Reaktion einer Verbindung der Formel

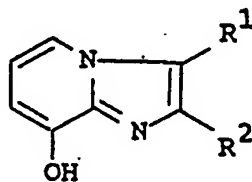


worin R^3 die oben genannte Bedeutung hat, oder eines Salzes davon, mit einer Verbindung der Formel



worin R^1 und R^2 jeweils wie oben definiert sind, oder mit dessen reaktionsfähigem Derivat an der Hydroxygruppe, oder

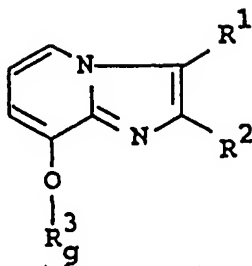
(2) Reaktion einer Verbindung der Formel



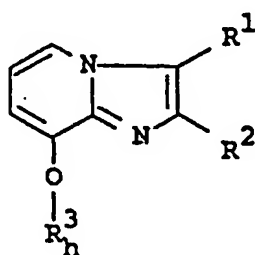
worin R^1 und R^2 jeweils wie oben definiert sind, oder eines Salzes davon, mit einer Verbindung der Formel

R^3 - OH

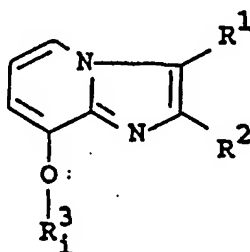
worin R^3 wie oben definiert ist, oder dessen reaktionsfähigem Derivat an der Hydroxygruppe, oder (3) eine Reduktionsreaktion einer Verbindung der Formel



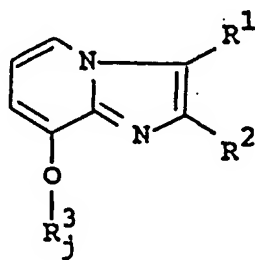
worin R^1 und R^2 jeweils wie oben definiert sind und R^3_g Benzyl ist, substituiert durch C_1 - C_6 -Alkyl und C_1 - C_6 -Alkanoylcarbonylamino, oder eines Salzes davon, um zu einer Verbindung der Formel



zu gelangen, worin R^1 und R^2 jeweils wie oben definiert sind und R^3_h Benzyl ist, substituiert durch C_1 - C_6 -Alkyl und α -Hydroxy(C_1 - C_6)alkanoylamino, oder einem Salz davon, oder
(4) eine Eliminierungsreaktion der Aminoschutzgruppe einer Verbindung der Formel



worin R^1 und R^2 jeweils wie oben definiert sind und R^3_i Benzyl ist, substituiert durch C_1 - C_6 -Alkyl und einen zusätzlichen Substituenten, ausgewählt unter C_1 - C_6 -Alkoxycarbonylamino(nieder)-alkanoylamino und 3-Benzoylthioureido, oder eines Salzes davon, um zu einer Verbindung der Formel

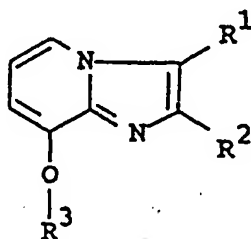


zu gelangen, worin R^1 und R^2 jeweils wie oben definiert sind und R^3 Benzyl ist, substituiert durch C_1 - C_6 -Alkyl und einen zusätzlichen Substituenten, ausgewählt unter Amino(C_1 - C_6)alkanoylamino und Thioureido, oder einem Salz davon.

- 5 5. Pharmazeutische Zusammensetzung, umfassend als aktiven Bestandteil eine Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon im Gemisch mit pharmazeutisch annehmbaren Trägern.
6. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon zur Verwendung als
10 Medikament.
7. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon zur Verwendung als ein Medikament zur Behandlung von Ulcus.

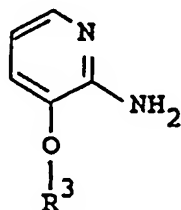
15 **Patentanspruch für folgenden Vertragsstaat : ES**

1. Verfahren zur Herstellung von Imidazopyridinverbindungen der Formel

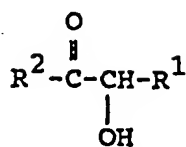


30 worin R^1 die Bedeutung C_2 - C_6 -Alkynyl hat, R^2 ist C_1 - C_6 -Alkyl und R^3 ist Benzyl substituiert durch C_1 - C_6 -Alkyl und einen zusätzlichen Substituenten, ausgewählt unter C_1 - C_6 -Alkanoylamino, C_1 - C_6 -Alkansulfonylamino, C_1 - C_6 -Alkoxy-carbonylamino, Isonicotinamido, Ureido, Ureido mit C_1 - C_6 -Alkyl, C_1 - C_6 -Alkoxy-carbonylamino(C_1 - C_6)alkanoylamino, Phenyl(C_1 - C_6)-alkoxy-carbonylamino, 3-Benzoylthioureido, Thioureido, C_1 - C_6 -Alkanoyloxy(C_1 - C_6)alkanoylamino, C_1 - C_6 -Alkanoylcarbonylamino, C_1 - C_6 -Alkoxy-carbonylcarbonylamino, Sulfamido, C_1 - C_6 -Alkanoylamino mit Hydroxy, und Amino(C_1 - C_6)alkanoylamino,
35 oder eines Salzes davon, umfassend

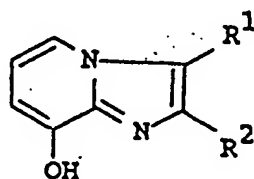
(1) die Reaktion einer Verbindung der Formel



50 worin R^3 die oben genannte Bedeutung hat, oder eines Salzes davon, mit einer Verbindung der Formel



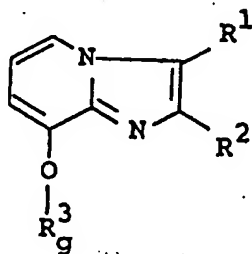
worin R¹ und R² jeweils wie oben definiert sind, oder mit dessen reaktionsfähigem Derivat an der Hydroxygruppe, oder
(2) Reaktion einer Verbindung der Formel



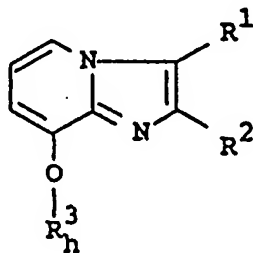
worin R¹ und R² jeweils wie oben definiert sind, oder eines Salzes davon, mit einer Verbindung der Formel

R³ - OH

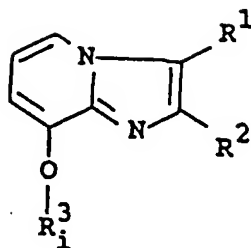
worin R³ wie oben definiert ist, oder dessen reaktionsfähigem Derivat an der Hydroxygruppe, oder
(3) eine Reduktionsreaktion einer Verbindung der Formel



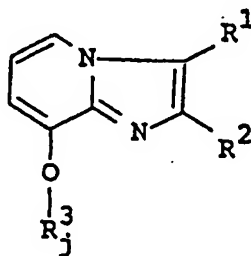
worin R¹ und R² jeweils wie oben definiert sind und R^{3g} Benzyl ist, substituiert durch C₁-C₆-Alkyl und C₁-C₆-Alkanoylcarbonylamino, oder eines Salzes davon, um zu einer Verbindung der Formel



zu gelangen, worin R¹ und R² jeweils wie oben definiert sind und R^{3h} Benzyl ist, substituiert durch C₁-C₆-Alkyl und α-Hydroxy(C₁-C₆)alkanoylamino, oder einem Salz davon, oder
(4) eine Eliminierungsreaktion der Aminoschutzgruppe einer Verbindung der Formel



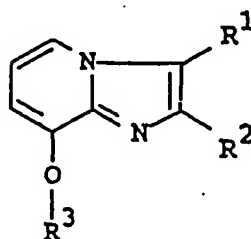
worin R^1 und R^2 jeweils wie oben definiert sind und R^3 , Benzyl ist, substituiert durch C_1 - C_6 -Alkyl und einen zusätzlichen Substituenten, ausgewählt unter C_1 - C_6 -Alkoxy-carbonylamino(nieder)-alkanoylamino und 3-Benzoylthioureido, oder eines Salzes davon, um zu einer Verbindung der Formel



zu gelangen, worin R^1 und R^2 jeweils wie oben definiert sind und R^3 , Benzyl ist, substituiert durch C_1 - C_6 -Alkyl und einen zusätzlichen Substituenten, ausgewählt unter Amino(C_1 - C_6)alkanoylamino und Thioureido, oder einem Salz davon.

Patentansprüche für folgenden Vertragsstaat : GR

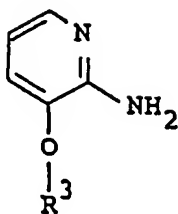
1. Verfahren zur Herstellung von Imidazopyridinverbindungen der Formel



worin R^1 die Bedeutung C_2 - C_6 -Alkynyl hat, R^2 ist C_1 - C_6 -Alkyl und R^3 ist Benzyl substituiert durch C_1 - C_6 -Alkyl und einen zusätzlichen Substituenten, ausgewählt unter C_1 - C_6 -Alkanoylamino, C_1 - C_6 -Alkansulfonylamino, C_1 - C_6 -Alkoxy-carbonylamino, Isonicotinamido, Ureido, Ureido mit C_1 - C_6 -Alkyl, C_1 - C_6 -Alkoxy-carbonylamino(C_1 - C_6)alkanoylamino, Phenyl(C_1 - C_6)-alkoxy-carbonylamino, 3-Benzoylthioureido, Thioureido, C_1 - C_6 -Alkanoyloxy(C_1 - C_6)alkanoylamino, C_1 - C_6 -Alkanoyl-carbonylamino, C_1 - C_6 -Alkoxy-carbonyl-carbonylamino, Sulfamido, C_1 - C_6 -Alkanoylamino mit Hydroxy, und Amino(C_1 - C_6)alkanoylamino, oder eines Salzes davon, umfassend

(1) die Reaktion einer Verbindung der Formel

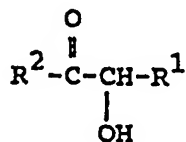
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worin R^3 die oben genannte Bedeutung hat, oder eines Salzes davon, mit einer Verbindung der Formel

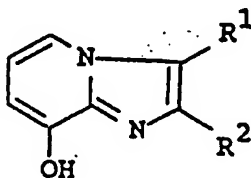
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worin R^1 und R^2 jeweils wie oben definiert sind, oder mit dessen reaktionsfähigem Derivat an der Hydroxygruppe, oder
(2) Reaktion einer Verbindung der Formel

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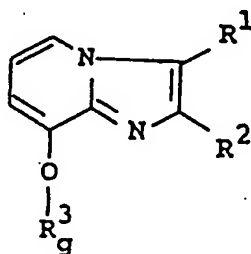
worin R^1 und R^2 jeweils wie oben definiert sind, oder eines Salzes davon, mit einer Verbindung der Formel

$R^3 - OH$

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worin R^3 wie oben definiert ist, oder dessen reaktionsfähigem Derivat an der Hydroxygruppe, oder
(3) eine Reduktionsreaktion einer Verbindung der Formel

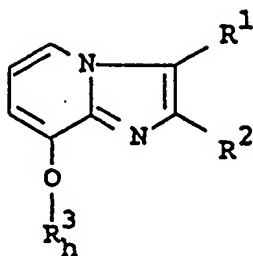
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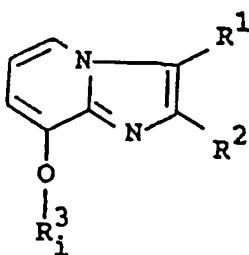
worin R^1 und R^2 jeweils wie oben definiert sind und R^3_g Benzyl ist, substituiert durch C_1-C_6 -Alkyl und C_1-C_6 -Alkanoylcarbonylamino, oder eines Salzes davon, um zu einer Verbindung der Formel



zu gelangen, worin R^1 und R^2 jeweils wie oben definiert sind und R^3_h Benzyl ist, substituiert durch C_1 - C_6 -Alkyl und α -Hydroxy(C_1 - C_6)alkanoylamino, oder einem Salz davon, oder

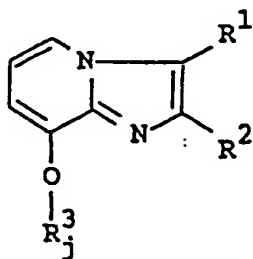
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(4) eine Eliminierungsreaktion der Aminoschutzgruppe einer Verbindung der Formel



worin R^1 und R^2 jeweils wie oben definiert sind und R^3_i Benzyl ist, substituiert durch C_1 - C_6 -Alkyl und einen zusätzlichen Substituenten, ausgewählt unter C_1 - C_6 -Alkoxycarbonylamino(nieder)-alkanoylamino und 3-Benzoylthioureido, oder eines Salzes davon, um zu einer Verbindung der Formel

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zu gelangen, worin R^1 und R^2 jeweils wie oben definiert sind und R^3_j Benzyl ist, substituiert durch C_1 - C_6 -Alkyl und einen zusätzlichen Substituenten, ausgewählt unter Amino(C_1 - C_6)alkanoylamino und Thioureido, oder einem Salz davon.

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2. Modifikation des Verfahrens nach Anspruch 1, gekennzeichnet dadurch, daß eine Verbindung, hergestellt nach einem Verfahren gemäß Anspruch 1, in eine pharmazeutisch annehmbare Form gebracht wird durch Vermischen oder Zubereiten der genannten Verbindung mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger.
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